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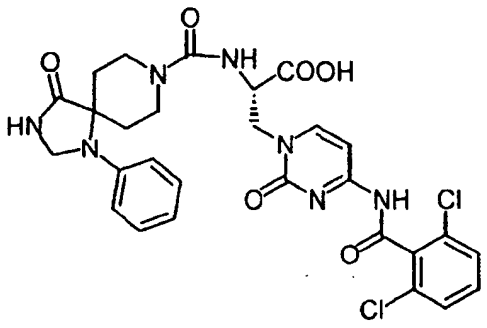
(54) UREA DERIVATIVE AND ADHESIVE-MOLECULE INHIBITOR CONTAINING THE SAME AS ACTIVE INGREDIENT

(57) Disclosed are novel urea derivatives and their medical uses, especially as adhesion molecule inhibitors useful for therapies of inflammatory diseases. The urea derivative according to the present invention has the chemical structure, for example, represented by the following Formula (35):



(35)

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Description

Technical Field

[0001] The present invention relates to an adhesion molecule inhibitor, especially VLA-4 inhibitor, containing a novel urea derivative or a pharmaceutically acceptable salt thereof, and to a medical use thereof, especially as a therapeutic agent against inflammatory diseases.

Background Art

[0002] Adhesion molecules participate in adhesion between cells and cells, and between cells and cell matrices. Adhesion molecules include a number of families such as integrin family and immunoglobulin super family. The adhesion molecules belonging to integrin family are those expressed on leukocytes such as lymphocytes, monocytes, basophils and eosinophils. These adhesion molecules have heterodimer structure, in which an α chain and a β chain are non-covalently bound, and are classified into some subfamilies depending on the species of the β chain. VLA-4 (very late antigen-4) also called α4β1 or CD49d/CD29, a member of the integrin family, participates in the interactions between leukocytes and vascular endothelial cells or extracellular matrix, and participates in infiltration of leukocytes into inflammatory site. VCAM-1 (vascular cell adhesion molecule-1) and fibronectin are known as the adhesion molecules which interact with VLA-4.

[0003] The binding site on fibronectin, which binds to VLA-4 is a fibronectin fragment called CS-1. It has been reported that the minimum unit required for the binding in this fragment consists of 3 amino acid residues, that is, Leucine-Aspartic acid-Valine.

[0004] Linear or cyclic peptidic VLA-4 adhesion inhibitor compounds based on the 3 amino acid residues, Leucine-Aspartic acid-Valine have been reported (WO/15973).

[0005] On the other hand, it is known that the expression level of VCAM-1 which is another adhesion molecule that also interacts with VLA-4, is increased by stimulation by a cytokine such as IL-1, TNF-α or IL-4, and that VCAM-1 interacts with VLA-4 existing on cells such as lymphocytes, NK cells, monocytes and eosinophils. VLA-4 and VCAM-1 participate in the infiltration of leukocytes into inflammatory sites through blood vessels. From this viewpoint, the interaction between VLA-4 and VCAM-1 is very important in inflammatory reaction.

[0006] Among the adhesion molecules, VCAM-1 belongs to the immunoglobulin super family, and 7-Ig-like-domain VCAM-1 and 6-Ig-like-domain VCAM-1 are known. Mutation experiments of VCAM-1 revealed that the binding sites on VCAM-1 for binding to VLA-4 are located in domain 1 and domain 4, and that the amino acid sequence of glutamine-isoleucine-aspartic acid-serine-proline on the CD loop is important for the binding to VLA-4 (e.g., J.Cell Biol., 124 , 601 (1994)). J.H.WANG et al. reported a cyclic peptide Cys*GlnIleAspSerProCys* (Cys*Cys* represents disulfide bond) which has an inhibitory activity against adhesion of VLA-4, which cyclic peptide is based on the glutamine-isoleucine-aspartic acid-serine-proline (Proc. Natl. Acad. Sci. USA , 92 , 5714 (1995)). Low molecular compounds having VLA-4-inhibitory activity have also been reported (e.g., US 5770573, US 5821231 and WO99/6436).

[0007] The fact that VLA-4 plays an important role in inflammatory reaction has been proved by experiments using anti-VLA-4 antibody in animal models such as contact hypersensitivity, delayed type hypersensitivity models (mouse and rat), experimental autoimmune encephalomyelitis models (mouse and rat), nephrotic nephritis (rat), passive cutaneous anaphylaxis model (guinea pig), immunocomplex-induced pulmonary injury model (rat), spontaneous colitis model (monkey), asthma model (sheep) and adjuvant arthritis model.

[0008] It has been proved that the cause of development of chronic inflammatory diseases such as allergic inflammation and chronic rheumatoid arthritis is the repetition of accumulation of leukocytes at the inflammatory site. However, as the drugs for the therapies of these diseases, drugs having activities to inhibit actions of chemical mediators, drugs having activities to inhibit production of chemical mediators, and drugs having activities to inhibit production of active oxygen are conventionally used. Drugs which inhibit activation of leukocytes, such as steroid drugs, are also used. Since these drugs do not have an activity to inhibit accumulation of leukocytes to the inflammatory site as their main actions, they cannot inhibit development of inflammation. In contrast, since adhesion molecules VLA-4 and VCAM-1 mainly participate in the process of accumulation of the leukocytes to the inflammatory site, a novel compound having an activity to inhibit the adhesion of VLA-4 and VCAM-1 is thought to inhibit the accumulation of the leukocytes to the inflammatory site. Thus, the probability that such a compound is an effective therapeutic drug against the above-mentioned diseases is high.

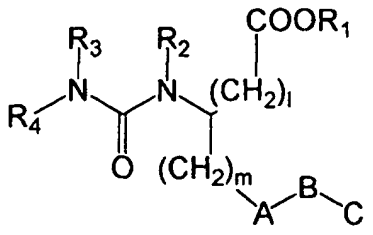
Disclosure of the Invention

[0009] An object of the present invention is to discover a compound which inhibits cell infiltration via adhesion molecules, especially, adhesion molecule VLA-4, thereby making it possible to prevent and cure inflammatory diseases

caused by infiltration of leukocytes such as monocytes, lymphocytes and eoshinophils.

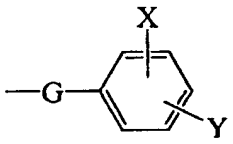
[0010] The present inventors intensively studied to discover that specific novel urea derivatives and pharmaceutically acceptable salts thereof have activities to inhibit cell adhesion via adhesion molecules, especially adhesion molecule VLA-4, thereby completing the present invention.

[0011] That is, the present invention provides a urea derivative of the Formula I:



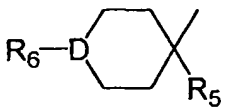
I

[wherein l represents an integer of 0 to 2; m represents an integer of 1 to 3; R_1 and R_2 independently represent hydrogen or C_1-C_6 linear alkyl; R_3 and R_4 independently represent hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole (excluding cases wherein C is represented by the Formula XIII:



XIII

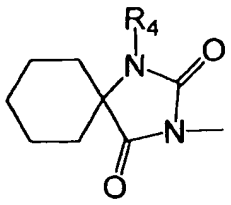
(wherein X and Y independently represent hydrogen, halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino or tetrazole; G may or may not exist, and when G exists, G is a nitrogen atom))
or represent Formula II:



II

(wherein D represents a carbon atom or nitrogen atom; R_5 represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear N-alkylcarboxamide, C_3-C_8 branched N-alkylcarboxamide, or phenyl or N-phenylcarboxamide, this phenyl or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole (with the proviso that when C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), R_5 is C_1-C_6 linear N-alkylcarboxamide, C_3-C_8 branched N-alkylcarboxamide or N-phenylcarboxamide substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole); R_6 represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, or phenylsulfone, benzoyl or benzyl, this phenylsulfone, benzoyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole) (with the proviso that when C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), R_6 is phenylsulfone, benzoyl or benzyl, this phenylsulfone, benzoyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of methyl, cyano, nitro, amino and tetrazole);

R_2 and R_3 may cooperatively represent Formula III:

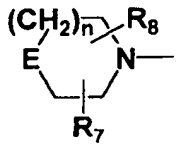


III

(wherein R_4 represents the same meanings as described above);
R_3 and R_4 may cooperatively represent

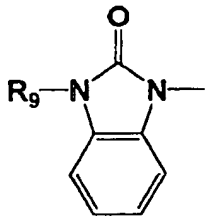
(i) Formula IV:

[0012]



IV

(wherein n represents an integer of 0 to 4; F represents a carbon atom or nitrogen atom; R_7 and R_8 independently represent hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, pyrrolidine carbonyl, piperidine carbonyl, or phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide, this phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole (with the proviso that when C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), R_7 and R_8 independently represent pyrrolidine carbonyl, piperidine carbonyl, or phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide, this phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of methyl, cyano, nitro, amino and tetrazole)
or Formula V:

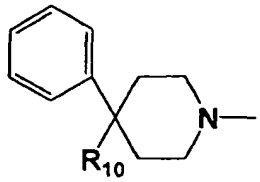


V

(wherein R_9 represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole),

(ii) Formula VI:

[0013]

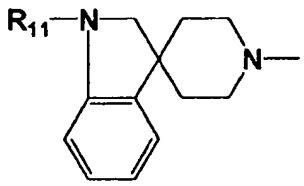


VI

(wherein R_{10} represents cyano, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylamide, C_3-C_8 branched alkylamide, C_5-C_7 cycloalkylamide, C_1-C_6 linear alkylsulfonylamine, C_3-C_8 branched alkylsulfonylamine, or benzamide, phenylsulfonylamine or benzylamino, this benzamide, phenylsulfonylamine or benzylamino being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole) (with the proviso that when C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), R_{10} is C_1-C_6 linear alkylsulfonylamine, C_3-C_8 branched alkylsulfonylamine, or phenylsulfonylamine substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole),

(iii) Formula VII:

[0014]

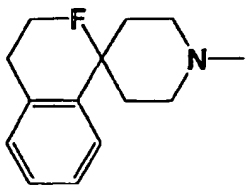


VII

(wherein R_1 represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, C_1-C_6 linear alkylsulfonyl, C_3-C_8 branched alkylsulfonyl, or phenylsulfonyl, benzyl or benzoyl, this phenylsulfonyl, benzyl or benzoyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole) (excluding cases where C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above)),

(iv) Formula VIII:

[0015]



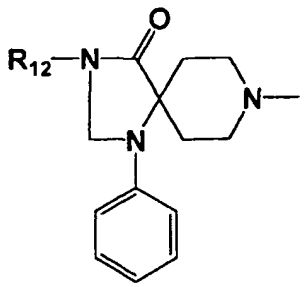
VIII

(wherein F represents a carbon atom, oxygen atom, sulfur atom or nitrogen atom; when F is a nitrogen atom, the

substituent on said nitrogen atom is hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, C_1-C_6 linear alkylsulfonyl, C_3-C_8 branched alkylsulfonyl, or phenylsulfonyl, benzyl or benzoyl, this phenylsulfonyl, benzyl or benzoyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole) (excluding cases where C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above)), or

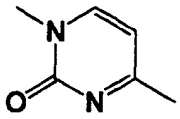
(v) Formula IX:

[0016]



IX

(wherein R_{12} represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_6-C_{10} alkylcycloalkyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole;
A is represented by Formula XI or XII:



XI

XII ;

B may or may not exist, when B exists, B represents amide or C_1-C_3 methylene chain;
C is represented by said Formula IV, VI, VII, VIII, IX or XIII (wherein symbols therein represent the same meanings as described above)],
or a pharmaceutically acceptable salt thereof.

[0017] The present invention also provides an adhesion molecule inhibitor comprising the urea derivative or a pharmaceutically acceptable salt thereof according to the present invention. The present invention further provides a medical use of the urea derivative or a pharmaceutically acceptable salt thereof according to the present invention, and especially, a therapeutic agent for inflammatory diseases. The present invention still further provides a method for inhibiting an adhesion molecule, comprising administering an effective amount of the urea derivative or a pharmaceutically acceptable salt thereof according to the present invention. The present invention still further provides a use of

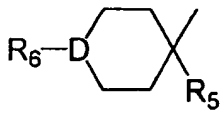
the urea derivative or a pharmaceutically acceptable salt thereof according to the present invention for the production of a pharmaceutical. The present invention still further provides a use of the urea derivative or a pharmaceutically acceptable salt thereof according to the present invention for the production of an adhesion molecule inhibitor.

[0018] By the present invention, novel substances having activities to inhibit cell adhesion via adhesion molecules, especially adhesion molecule VLA-4, were provided. Since the urea derivatives according to the present invention are excellent in inhibiting cell adhesion via adhesion molecules, they are useful as therapeutic drugs against various inflammatory diseases.

Best Mode for Carrying Out the Invention

[0019] As mentioned above, the urea derivatives according to the present invention are represented by Formula I. In Formula I, 1 represents an integer of 0 to 2; m represents an integer of 1 to 3; R_1 and R_2 independently represent hydrogen or C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl; R_3 and R_4 independently represent hydrogen, C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl or 4,5-dimethylhexyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole (excluding cases wherein C is represented by the Formula XIII), such as phenyl, 2-cyanophenyl, 2-hydroxyphenyl, 2-chlorophenyl, 2-nitrophenyl, 2-aminophenyl, 2-bromophenyl, 2-fluorophenyl, 2-tetrazoylphenyl, 2,6-dihydroxyphenyl, 2,6-dimethoxyphenyl, 2,6-dichlorophenyl, 2,6-dinitrophenyl, 2,6-dimethylphenyl, benzyl, 2-cyanobenzyl, 2-hydroxybenzyl, 2-chlorobenzyl, 2-nitrobenzyl, 2-aminobenzyl, 2-bromobenzyl, 2-fluorobenzyl, 2-tetrazoylbenzyl, 2,6-dihydroxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-dinitrobenzyl or 2,6-dimethylbenzyl,

Formula II:

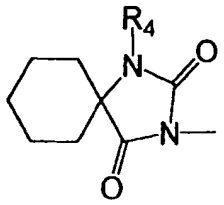


II

(wherein D represents a carbon atom or nitrogen atom; R_5 represents hydrogen, C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl or 4,5-dimethylhexyl, C_1-C_6 linear N-alkylcarboxamide such as N-methylcarboxamide, N-ethylcarboxamide or N-(n-propyl)carboxamide, C_3-C_8 branched N-alkylcarboxamide such as N-isopropylcarboxamide, N-isobutylcarboxamide, N-isopentylcarboxamide or N-isohexylcarboxamide, or phenyl or N-phenylcarboxamide, this phenyl or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, such as phenyl, 2-cyanophenyl, 2-hydroxyphenyl, 2-chlorophenyl, 2-nitrophenyl, 2-aminophenyl, 2-bromophenyl, 2-fluorophenyl, 2-tetrazoylphenyl, 2,6-dihydroxyphenyl, 2,6-dimethoxyphenyl, 2,6-dichlorophenyl, 2,6-dinitrophenyl, 2,6-dimethylphenyl, N-phenylcarboxamide, N-(2-cyanophenyl)carboxamide, N-(2-hydroxyphenyl)carboxamide, N-(2-chlorophenyl)carboxamide, N-(2-nitrophenyl)carboxamide, N-(2-aminophenyl)carboxamide, N-(2-brompphenyl)carboxamide, N-(2-fluorophenyl)carboxamide, N-(2-tetrazoylphenyl)carboxamide, N-(2,6-dihydroxyphenyl)carboxamide, N-(2,6-dimethoxyphenyl)carboxamide, N-(2,6-dichlorophenyl)carboxamide, N-(2,6-dinitro)phenylcarboxamide or N-(2,6-dimethylphenyl)carboxamide (with the proviso that when C is represented by said Formula XIII, R_5 is C_1-C_6 linear N-alkylcarboxamide, C_3-C_8 branched N-alkylcarboxamide or N-phenylcarboxamide substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole);

R_6 represents hydrogen, C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl or 4,5-dimethylhexyl, C_1-C_6 linear alkylacyl such as acetyl, propionyl, butyryl or valeryl, C_3-C_8 branched alkylacyl such as isopropionyl, isobutyryl, pivaloyl or isopentanoyl, or phenylsulfone, benzoyl or benzyl, this phenylsulfone, benzoyl or benzyl being substituted with 0 to 2 substituents selected

from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, such as phenylsulfonyl, 2-cyanophenylsulfonyl, 2-hydroxyphenylsulfonyl, 2-chlorophenylsulfonyl, 2-nitrophenylsulfonyl, 2-aminophenylsulfonyl, 2-bromophenylsulfonyl, 2-fluorophenylsulfonyl, 2-tetrazoylphenylsulfonyl, 2,6-dihydroxyphenylsulfonyl, 2,6-dimethoxyphenylsulfonyl, 2,6-dichlorophenylsulfonyl, 2,6-dinitrophenylsulfonyl, 2,6-dimethylphenylsulfonyl, benzoyl, 2-cyanobenzoyl, 2-hydroxybenzoyl, 2-chlorobenzoyl, 2-nitrobenzoyl, 2-aminobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-tetrazoylbenzoyl, 2,6-dihydroxybenzoyl, 2,6-dimethoxybenzoyl, 2,6-dichlorobenzoyl, 2,6-dinitrobenzoyl, 2,6-dimethylbenzoyl, benzyl, 2-cyanobenzyl, 2-hydroxybenzyl, 2-chlorobenzyl, 2-nitrobenzyl, 2-aminobenzyl, 2-bromobenzyl, 2-fluorobenzyl, 2-tetrazoylbenzyl, 2,6-dihydroxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-dinitrobenzyl or 2,6-dimethylbenzyl (with the proviso that when C is represented by said Formula XIII, R_6 is phenylsulfone, benzyl or benzyl, this phenylsulfone, benzyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of methyl, cyano, nitro, amino and tetrazole);
R_2 and R_3 may cooperatively represent Formula III:

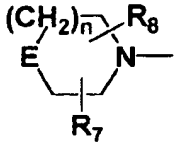


III

(wherein R_4 represents the same meanings as described above);
R_3 and R_4 may cooperatively represent

(i) Formula IV:

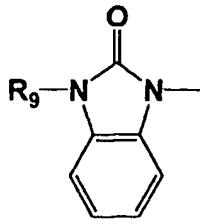
[0020]



IV

(wherein n represents an integer of 0 to 4; E represents a carbon atom or nitrogen atom; R_7 and R_8 independently represent hydrogen, C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl or 4,5-dimethylhexyl, C_1-C_6 linear alkylacyl such as acetyl, propionyl, butyryl or valeryl, C_3-C_8 branched alkylacyl such as isopropionyl, isobutyryl, pivaloyl or isopentanoyl, pyrrolidine carbonyl, piperidine carbonyl, or phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide, this phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, such as phenyl, 2-cyanophenyl, 2-hydroxyphenyl, 2-chlorophenyl, 2-nitrophenyl, 2-aminophenyl, 2-bromophcnyl, 2-fluorophenyl, 2-tetrazoylphenyl, 2,6-dihydroxyphenyl, 2,6-dimethoxyphenyl, 2,6-dichlorophenyl, 2,6-dinitrophenyl, 2,6-dimethylphenyl, benzoyl, 2-cyanobenzoyl, 2-hydroxybenzoyl, 2-chlorobenzoyl, 2-nitrobenzoyl, 2-aminobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-tetrazoylbenzoyl, 2,6-dihydroxybenzoyl, 2,6-dimethoxybenzoyl, 2,6-dichlorobenzoyl, 2,6-dinitrobenzoyl, 2,6-dimethylbenzoyl, benzyl, 2-cyanobenzyl, 2-hydroxybenzyl, 2-chlorobenzyl, 2-nitrobenzyl, 2-aminobenzyl, 2-bromobenzyl, 2-fluorobenzyl, 2-tetrazoylbenzyl, 2,6-dihydroxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-dinitrobenzyl, 2,6-dimethylbenzyl, benzamide, 2-cyanobenzamide, 2-hydroxybenzamide, 2-chlorobenzamide, 2-nitrobenzamide, 2-aminobenzamide, 2-bromobenzamide, 2-fluorobenzamide, 2-tetrazoylbenzamide, 2,6-dihydroxybenzamide, 2,6-dimethoxybenzamide, 2,6-dichlorobenzamide, 2,6-dinitrobenzamide, 2,6-dimethylbenzamide, N-phenylcarboxamide, N-(2-cyanophenyl)carboxamide, N-(2-hydroxyphenyl)carboxamide,

N-(2-chlorophenyl)carboxamide, N-(2-nitrophenyl)carboxamide, N-(2-aminophenyl)carboxamide, N-(2-bromophenyl) carboxamide, N-(2-fluorophenyl)carboxamide, N-(2-tetrazoylphenyl)carboxamide, N-(2,6-dihydroxyphenyl)carboxamide, N-(2,6-dimethoxyphenyl)carboxamide, N-(2,6-dichlorophenyl)carboxamide, N-(2,6-dinitro)phenylcarboxamide or N-(2,6-dimethylphenyl)carboxamide (with the proviso that when C is represented by said Formula XIII, R_7 and R_8 independently represent pyrrolidine carbonyl, piperidine carbonyl, or phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide, this phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of methyl, cyano, nitro, amino and tetrazole),
or Formula V:

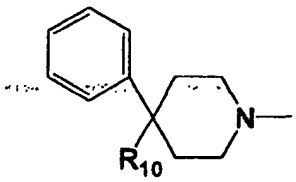


V

(wherein R_9 represents hydrogen, C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl, 4,5-dimethylhexyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, such as phenyl, 2-cyanophenyl, 2-hydroxyphenyl, 2-chlorophenyl, 2-nitrophenyl, 2-aminophenyl, 2-bromophenyl, 2-fluorophenyl, 2-tetrazoylphenyl, 2,6-dihydroxyphenyl, 2,6-dimethoxyphenyl, 2,6-dichlorophenyl, 2,6-dinitrophenyl, 2,6-dimethylphenyl, benzyl, 2-cyanobenzyl, 2-hydroxybenzyl, 2-chlorobenzyl, 2-nitrobenzyl, 2-aminobenzyl, 2-bromobenzyl, 2-fluorobenzyl, 2-tetrazoylbenzyl, 2,6-dihydroxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-dinitrobenzyl or 2,6-dimethylbenzyl,

(ii) Formula VI:

[0021]



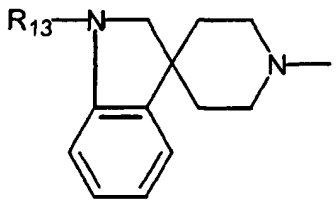
VI

(wherein R_{10} represents cyano, C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl or 4,5-dimethylhexyl, C_1-C_6 linear alkylacyl, that is, acetyl, propionyl, butyryl, valeryl, pentanoyl or hexanoyl, C_3-C_8 branched alkylacyl such as isopropionyl, isobutyryl, pivaloyl, isopentanoyl, isohexanoyl or isoheptanoyl, C_5-C_7 cycloalkylamide such as cyclopentylamide or cyclohexylamide, C_1-C_6 linear alkylsulfonylamine, that is, methylsulfonylamine, ethylsulfonylamine, n-propylsulfonylamine, n-butylsulfonylamine, n-pentylsulfonylamine or n-hexylsulfonylamine, C_3-C_8 branched alkylsulfonylamine such as isopropylsulfonylamine, isobutylsulfonylamine, t-butylsulfonylamine, isopentylsulfonylamine, isohexylsulfonylamine or isoheptylsulfonylamine, or benzamide, phenylsulfonylamine or benzylamide, this benzamide, phenylsulfonylamine or benzylamide

being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, such as benzamide, 2-cyanobenzamide, 2-hydroxybenzamide, 2-chlorobenzamide, 2-nitrobenzamide, 2-aminobenzamide, 2-bromobenzamide, 2-fluorobenzamide, 2-tetrazoylbenzamide, 2,6-dihydroxybenzamide, 2,6-dimethoxybenzamide, 2,6-dichlorobenzamide, 2,6-dinitrobenzamide, 2,6-dimethylbenzamide, benzylamide, 2-cyanobenzylamide, 2-hydroxybenzylamide, 2-chlorobenzylamide, 2-nitrobenzylamide, 2-aminobenzylamide, 2-bromobenzylamide, 2-fluorobenzylamide, 2-tetrazoylbenzylamide, 2,6-dihydroxybenzylamide, 2,6-dimethoxybenzylamide, 2,6-dichlorobenzylamide, 2,6-dinitrobenzylamide, 2,6-dimethylbenzylamide, phenylsulfonylamine, 2-cyanophenylsulfonylamine, 2-hydroxyphenylsulfonylamine, 2-chlorophenylsulfonylamine, 2-nitrophenylsulfonylamine, 2-aminophenylsulfonylamine, 2-bromophenylsulfonylamine, 2-fluorophenylsulfonylamine, 2-tetrazoylphenylsulfonylaminc, 2,6-dihydroxyphenylsulfonylamine, 2,6-dimethoxyphenylsulfonylamine, 2,6-dichlorophenylsulfonylamine, 2,6-dinitrophenylsulfonylamine or 2,6-dimethylphenylsulfonylamine (with the proviso that when C is represented by said Formula XIII, R_{10} is C_1-C_6 linear alkylsulfonylamine, C_3-C_8 branched alkylsulfonylamine, or phenylsulfonylamine substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole),

(iii) Formula VII:

[0022]

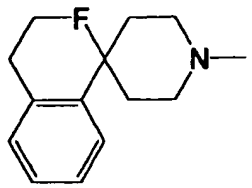


VII

(wherein R_{11} represents hydrogen, C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl or 4,5-dimethylhexyl, C_1-C_6 linear alkylacyl, that is, acetyl, propionyl, butyryl, valeryl, pentanoyl or hexanoyl, C_3-C_8 branched alkylacyl such as isopropionyl, isobutyryl, pivaloyl, isopentanoyl, isohexanoyl or isoheptanoyl, C_1-C_6 linear alkylsulfonyl, that is, mesyl, ethanesulfonyl, n-propanesulfonyl, n-butanesulfonyl, n-pentanesulfonyl or n-hexanesulfonyl, C_3-C_8 branched alkylsulfonyl such as isopropanesulfonyl, isobutanesulfonyl, t-butanesulfonyl, isopentanesulfonyl, isohexanesulfonyl or isoheptanesulfonyl, or phenylsulfonyl, benzyl or benzoyl, this phenylsulfonyl, benzyl or benzoyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, such as benzyl, 2-cyanobenzyl, 2-hydroxybenzyl, 2-chlorobenzyl, 2-nitrobenzyl, 2-aminobenzyl, 2-bromobenzyl, 2-fluorobenzyl, 2-tetrazoylbenzyl, 2,6-dihydroxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-dinitrobenzyl or 2,6-dimethylbenzyl, phenylsulfonyl, 2-cyanophenylsulfonyl, 2-hydroxyphenylsulfonyl, 2-chlorophenylsulfonyl, 2-nitrophenylsulfonyl, 2-aminophenylsulfonyl, 2-bromophenylsulfonyl, 2-fluorophenylsulfonyl, 2-tetrazoylphenylsulfonyl, 2,6-dihydroxyphenylsulfonyl, 2,6-dimethoxyphenylsulfonyl, 2,6-dichlorophenylsulfonyl, 2,6-dinitrophenylsulfonyl, 2,6-dimethylphenylsulfonyl, benzoyl, 2-cyanobenzoyl, 2-hydroxybenzoyl, 2-chlorobenzoyl, 2-nitrobenzoyl, 2-aminobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-tetrazoylbenzoyl, 2,6-dihydroxybenzoyl, 2,6-dimethoxybenzoyl, 2,6-dichlorobenzoyl, 2,6-dinitrobenzoyl or 2,6-dimethylbenzoyl (excluding cases where C is represented by said Formula XIII),

(iv) Formula VIII:

[0023]

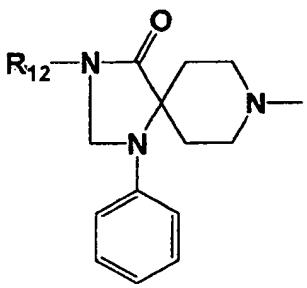


VIII

(wherein F represents a carbon atom, oxygen atom, sulfur atom or nitrogen atom; when F is a nitrogen atom, the substituent on said nitrogen atom is C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl or 4,5-dimethylhexyl, C_1-C_6 linear alkylacyl, that is, acetyl, propionyl, butyryl, valeryl, pentanoyl or hexanoyl, C_3-C_8 branched alkylacyl such as isopropionyl, isobutyryl, pivaloyl, isopentanoyl, isohexanoyl or isoheptanoyl, C_1-C_6 linear alkylsulfonyl, that is, mesyl, ethanesulfonyl, n-propanesulfonyl, n-butanesulfonyl, n-pentanesulfonyl or n-hexanesulfonyl, C_3-C_8 branched alkylsulfonyl such as isopropanesulfonyl, isobutanesulfonyl, t-butanesulfonyl, isopentanesulfonyl, isohexanesulfonyl or isoheptanesulfonyl, or phenylsulfonyl, benzyl or benzoyl, this phenylsulfonyl, benzyl or benzoyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, such as benzyl, 2-cyanobenzyl, 2-hydroxybenzyl, 2-chlorobenzyl, 2-nitrobenzyl, 2-aminobenzyl, 2-bromobenzyl, 2-fluorobenzyl, 2-tetrazoylbenzyl, 2,6-dihydroxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-dinitrobenzyl or 2,6-dimethylbenzyl, phenylsulfonyl, 2-cyanophenylsulfonyl, 2-hydroxyphenylsulfonyl, 2-chlorophenylsulfonyl, 2-nitrophenylsulfonyl, 2-aminophenylsulfonyl, 2-bromophenylsulfonyl, 2-fluorophenylsulfonyl, 2-tetrazoylphenylsulfonyl, 2,6-dihydroxyphenylsulfonyl, 2,6-dimethoxyphenylsulfonyl, 2,6-dichlorophenylsulfonyl, 2,6-dinitrophenylsulfonyl, 2,6-dimethylphenylsulfonyl, benzoyl, 2-cyanobenzoyl, 2-hydroxybenzoyl, 2-chlorobenzoyl, 2-nitrobenzoyl, 2-aminobenzoyl, 2-bromobenzoyl, 2-fluorobenzoyl, 2-tetrazoylbenzoyl, 2,6-dihydroxybenzoyl, 2,6-dimethoxybenzoyl, 2,6-dichlorobenzoyl, 2,6-dinitrobenzoyl or 2,6-dimethylbenzoyl (excluding cases where C is represented by said Formula XIII),

(v) Formula IX:

[0024]

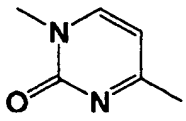


IX

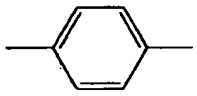
(wherein R_{12} represents C_1-C_6 linear alkyl, that is, methyl, ethyl, n-propyl, n-butyl, n-pentyl or n-hexyl, C_3-C_8 branched alkyl such as 1-methylethyl, 1-methylpropyl, 2-methylpropyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1-methylhexyl, 2-methylhexyl, 3-methylhexyl, 4-methylhexyl, 5-methylhexyl, 3,5-dimethylhexyl, 3,6-dimethylhexyl or 4,5-dimethylhexyl, C_6-C_{10} alkylcycloalkyl such as cyclopentylmethyl, cyclohexylmethyl or cycloheptylmethyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetra-

zole, such as phenyl, 2-cyanophenyl, 2-hydroxyphenyl, 2-chlorophenyl, 2-nitrophenyl, 2-aminophenyl, 2-bromophenyl, 2-fluorophenyl, 2-tetrazoylphenyl, 2,6-dihydroxyphenyl, 2,6-dimethoxyphenyl, 2,6-dichlorophenyl, 2,6-dinitrophenyl, 2,6-dimethylphenyl, benzyl, 2-cyanobenzyl, 2-hydroxybenzyl, 2-chlorobenzyl, 2-nitrobenzyl, 2-aminobenzyl, 2-bromobenzyl, 2-fluorobenzyl, 2-tetrazoylbenzyl, 2,6-dihydroxybenzyl, 2,6-dimethoxybenzyl, 2,6-dichlorobenzyl, 2,6-dinitrobenzyl or 2,6-dimethylbenzyl);

A is represented by Formula XI or XII:



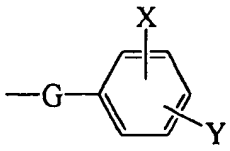
XI



XII ;

B may or may not exist, when B exists, B represents amide or C_1-C_3 methylene chain;

C is represented by said Formula IV, VI, VII, VIII, IX or XIII



XIII

(wherein X and Y represent the same meanings as described above; G may or may not exist, and when G exists, G is a nitrogen atom)]

or a pharmaceutically acceptable salt thereof.

[0025] In the definitions of each substituents, the phrase that a certain group does "not exist" or "no group" exists means that the group is "not shown in the structural formula", and includes the both cases where atom(s) actually does (do) not exist and hydrogen atom(s) exist(s). For example, in Formula I, in case where B does not exist, it means that A and C are directly bonded. On the other hand, for example, in Formula XIII, in case where G is a nitrogen atom, it means that one hydrogen atom is bound to G. Those skilled in the art can easily and definitely understand what a specific structural formula mean.

[0026] Specific examples of the compounds according to the present invention include 3-(4-((2,6-dichlorophenyl) carbonylamino)-2-oxohydropyrimidinyl)-2-((ethylamino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((ethylamino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((ethylamino)carbonylamino)propanoic acid, 3 -(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((dimethylamino)carbonylamino)propanoic acid, 3-(4-((2,6-dimeththylphenyl) carbonylamino)-2-oxohydropyrimidinyl)-2-((dimethylamino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl) carbonylamino)-2-oxohydropyrimidinyl)-2-((dimethylamino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl) carbonylamino)-2-oxohydropyrimidinyl)-2-((methyl(methylethyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methyl(methylethyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methyl(methylethyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methylphenylami-

no)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methylphenylamino)carbonylamino)propanoicacid,3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methylphenylamino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-phenyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-phenyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoicacid,3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-phenyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-methyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-methyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoicacid,3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-methyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-acetyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-acetyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-acetyl-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-(2-methylpropyl)-4-(2-methylpropanoyl)-4-piperidyl)amino)carbonylamino)propanoicacid,3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-(2-methylpropyl)-4-(2-methylpropanoyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-(2-methylpropyl)-4-(2-methylpropanoyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-acetyl-1-(phenylcarbonyl)-4-piperidyl)amino)carbonylamino)propanoicacid,3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-acetyl-1-(phenylcarbonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-acetyl-1-(phenylcarbonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-ethyl-1-(2-methylpropanoyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-ethyl-1-(2-methylpropanoyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-ethyl-1-(2-methylpropanoyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropanoyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropanoyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropanoyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(phenylcarbonyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(phenylcarbonyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(phenylcarbonyl)-1-benzyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-methyl-4-(phenylcarbonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-methyl-4-(phenylcarbonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((1-methyl-4-(phenylcarbonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropanoyl)-1-phenyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropanoyl)-1-phenyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(2-methylpropanoyl)-1-phenyl-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-(phenylsulfonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-acetyl-1-(phenylsulfonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-acetyl-1-(phenylsulfonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-ethyl-1-(phenylsulfonyl)-4-piperidyl)amino)carbonylamino)propanoicacid,3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-ethyl-1-(phenylsulfonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-ethyl-1-(phenylsulfonyl)-4-piperidyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(piperidylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(piperidyl-

carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(piperidylcarbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(pyrrolidinylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(pyrrolidinylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(pyrrolidinylcarbonylamino)propanoic acid, 2-(azaperhydroepinylcarbonylamino)-3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-(azaperhydroepinylcarbonylamino)-3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-(azaperhydroepinylcarbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethylpiperidyl)carbonylamino)propanoic acid, 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panoylamino)cyclohexyl)amino)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-benzyl-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-benzyl-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-benzyl-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(acetylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(acetylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(acetylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((methylethyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((methylethyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid. 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((methylethyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methylbutanoylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methylbutanoylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methylbutanoylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((methylsulfonyl)amino)-4-phenylpiperidyl)carbonylamino)propanoicacid,3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((methylsulfonyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((methylsulfonyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(((methylethyl)sulfonyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(((methylethyl)sulfonyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(((methylethyl)sulfonyl)amino)-4-phenylpiperidyl)carbonylamino)propanoicacid,3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((phenylsulfonyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((phenylsulfonyl)amino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((phenylsulfonyl)amino)-4-phenylpiperidyl)carbonylamino) propanoic acid, 2-((2,4,8-triaza-2-methyl-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-2-methyl-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-2-methyl-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenylspiro [4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-2-(2-methylpropyl)-1-oxo-4-phenylspiro [4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-2-(2-methylpropyl)-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3 -(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-2-(2-methylpropyl)-1-oxo-4-phenylspiro [4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenyl-2-benzylspiro[4.5]dec-8-yl)carbonylamino)-3 -(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenyl-2-benzylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenyl-2-benzylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-2,4-diphenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-2,4-diphenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-' dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-2,4-diphenylspiro[4.5]dec-8-yl)carbonylamino)-

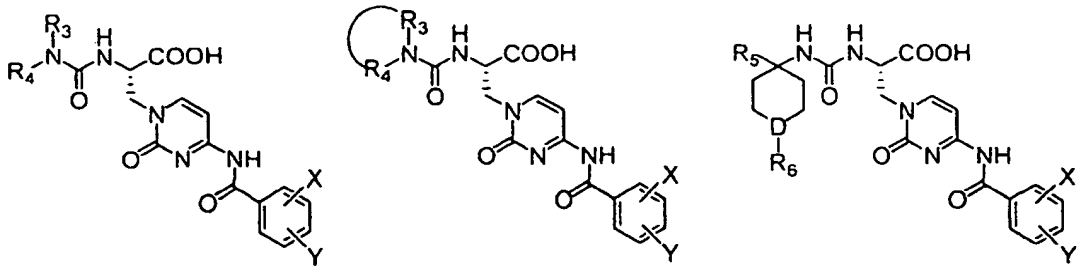
3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenyl-spiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl))carbonylamino)-2-oxohydropyrimidinyl)propanoicacid,2-((2,4,8-triaza-2-methyl-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,4,8-triaza-2-methyl-1-oxo-4-phenylspiro[4.5]dec-8-yl))carbonylamino)-2-oxohydropyrimidinyl)propanoicacid,3-(4-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl))carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethoxyphenyl)carbonylamino)propanoic acid, 3-(4-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl))carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethylphenyl)carbonylamino)propanoic acid, 3-(4-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl))carbonyl amino)-2-oxohydropyrimidinyl)-2-((2,6-dichlorophenyl)carbonylamino)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(2-oxo-4-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(2-oxo-4-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(2-oxo-4-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(2-oxo-4-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(2-oxo-4-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(2-oxo-4-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(4-((4-((acetylamino)-4-phenyl-piperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(4-((4-((acetylamino)-4-phenylpiperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(4-((4-((acetylamino)-4-phenylpiperidyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(4-((4-((acetylamino)-4-phenylpiperidyl)carbonylamino)phenyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(4-((4-((acetylamino)-4-phenylpiperidyl)carbonylamino)phenyl) propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(4-((4-((acetylamino)-4-phenylpiperidyl)carbonylamino)phenyl)propanoic acid, 3-(4-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)phenyl)-2-((2,6-dichlorophenyl)carbonylamino)propanoic acid, 3-(4-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)phenyl)-2-((2,6-dimethylphenyl)carbonylamino)propanoic acid, 3-(4-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)phenyl)-2-((2,6-dimethoxyphenyl)carbonylamino)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5] dec-8-yl)carbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dimethylphenyl)carbonylamino) phenyl)propanoic acid, 2-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dimethoxyphenyl)carbonylamino) phenyl) propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)phenyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)phenyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl)-2-((4-(acetylamino)-4-phenylpiperidyl) carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)phenyl)-2-((4-(acetylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)phenyl)-2-((4-(acetylamino)-4-phenyl-piperidyl)carbonylamino)propanoic acid, 2-(2,4-diaza-1,3-dioxospiro[4.5]dec-2-yl)-3-(4-((2,6-dimethoxyphenyl)carbonylamino)phenyl)propanoic acid, 2-(2,4-diaza-1,3-dioxospiro[4.5]dec-2-yl)-3-(4-((2,6-dimethylphenyl)carbonylamino) phenyl)propanoic acid, 2-(2,4-diaza-1,3-dioxospiro[4.5]dec-2-yl)-3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl) propanoic acid, 2-(2,4-diaza-4-methyl-1,3-dioxospiro[4.5]dec-2-yl)-3-(4-((2,6-dimethoxyphenyl)carbonylamino)phenyl)propanoic acid, 2-(2,4-diaza-4-methyl-1,3-dioxospiro[4.5]dec-2-yl)-3-(4-((2,6-dimethylphenyl)carbonylamino)phenyl)propanoic acid, 2-(2,4-diaza-4-methyl-1,3dioxospiro[4.5]dec-2-yl)-3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl)propanoic acid, 2-(2,4-diaza-1,3-dioxo-4-benzylspiro[4.5]dec-2-yl)-3-(4-((2,6-dimethoxyphenyl)carbonylamino) phenyl)propanoic acid, 2-(2,4-diaza-1,3-dioxo-4-benzylspiro[4.5]dec-2-yl)-3-(4-((2,6-dimethylphenyl)carbonylamino) phenyl)propanoic acid, 2-(2,4-diaza-1,3-dioxo-4-benzylspiro[4.5]dec-2-yl)-3-(4-((2,6-dichlorophenyl)carbonylamino) phenyl)propanoic acid, 3 -(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(indoline-3,4'-piperidine)-10-ylcarbonylamino)propanoic acid, 3 -(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(indoline-3,4'-piperidine)-10-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(indoline-3,4'-piperidine)-10-ylcarbonylamino)propanoicacid,3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-methylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-methylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-methylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(methylsulfonyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(methylsulfonyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(methylsulfonyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl) carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylsulfonyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylsulfonyl)spiro(indoline-

3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylsulfonyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylcarbonyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylcarbonyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylcarbonyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(2-methylpropyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(2-methylpropyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(2-methylpropyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-propanoylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-propanoylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-propanoylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(2-methylpropanoyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(2-methylpropanoyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(2-methylpropanoyl)spiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-phenylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-phenylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-phenylspiro(indoline-3,4'-piperidine)-10-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(isochromanl,4'-piperidine)-11-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(isochroman1,4'-piperidine)-11-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(isochroman1,4'-piperidine)-11-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(3H,4H-benzo[b]thian-1,4'-piperidine)-11-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(3H,4H-benzo[b]thian-1,4'-piperidine)-11-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(3H,4H-benzo[b]thian-1,4'-piperidine)-11-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-1-ylcarbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-methylspiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl) carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-methylspiro (1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-methylspiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 2-((acetylspiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((acetylspiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((acetylspiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-1-yl)carbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylcarbonyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl) carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylcarbonyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylcarbonyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(methylsulfonyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(methylsulfonyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(methylsulfonyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylsulfonyl)spiro (1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylsulfonyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl) carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylsulfonyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(3-methylbutanoyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperid-

ine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethylphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(3-methylbutanoyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 3-(4-((2,6-dimethoxyphenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(3-methylbutanoyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(4-((2-(methanesulfonyl)spiro(isoindoline-1,4'-piperidine)-10-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(4-((2-(methanesulfonyl)spiro(isoindoline-1,4'-piperidine)-10-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(4-((2-(methanesulfonyl)spiro(isoindoline-1,4'-piperidine)-10-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(2-oxo-4-(spiro(isochroman-1,4'-piperidine-11-ylcarbonylamino)hydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(2-oxo-4-(spiro(isochroman-1,4'-piperidine-11-ylcarbonylamino)hydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(2-oxo-4-(spiro(isochroman-1,4'-piperidine-11-ylcarbonylamino)hydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(2-oxo-4-(spiro(3H,4H-benzo [d]thian-1,4'-piperidine-11-ylcarbonylamino)hydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(2-oxo-4-(spiro(3H,4H-benzo[d]thian-1,4'-piperidine-11-ylcarbonylamino)hydropyrimidinyl)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(2-oxo-4-(spiro(3H,4H-benzo[d]thian-1,4'-piperidine-11-ylcarbonylamino) hydropyrimidinyl)propanoic acid, 3-(4-((2-acetylspiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dichlorophenyl)carbonylamino)propanoic acid, 3-(4-((2-acetylspiro (1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethylphenyl) carbonylamino)propanoic acid, 3 -(4-((2-acetylspiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethoxyphenyl)carbonylamino)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(4-((2-(2-methylpropanoyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(4-((2-(2-methylpropanoyl)spire (1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(4-((2-(2-methylpropanoyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)- 11-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(2-oxo-4-((2-(phenylcarbonyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)hydropyrimidinyl) propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(2-oxo-4-((2-(phenylcarbonyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)hydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(2-oxo-4-((2-(phenylcarbonyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino) hydropyrimidinyl)propanoic acid, 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(4-((2-(methylsulfonyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(4-((2-(methylsulfonyl)spire(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(4-((2-(methylsulfonyl)spire (1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid, 2-((2,6-dichlorophenyl)carbonylamino)-3-(2-oxo-4-((2-(phenylsulfonyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)hydropyrimidinyl)propanoic acid, 2-((2,6-dimethylphenyl)carbonylamino)-3-(2-oxo-4-((2-(phenylsulfonyl)spiro(1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)hydropyrimidinyl)propanoic acid, and 2-((2,6-dimethoxyphenyl)carbonylamino)-3-(2-oxo-4-((2-(phenylsulfonyl)spiro (1,2,3,4-tetrahydroisoquinoline-1,4'-piperidine)-11-yl)carbonylamino)hydropyrimidinyl)propanoic acid.

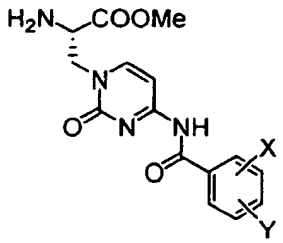
[0027] The processes for producing the compounds represented by Formula I (hereinafter, for example, "the compounds represented by Formula I" may also be indicated simply as "Formula I") will now be described. However, the process for producing each of the compounds is not restricted to that described herein In the various production processes, the reaction conditions may be appropriately selected from those described below.

[0028] Among the compounds represented by Formula I, those wherein l=0, m=1, R_1 and R_2 are hydrogen atoms, A is Formula XI, B is amide, C is Formula XIII, G does not exist, R_3 and R_4 are independently hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, or phenyl or benzyl, which phenyl or benzyl are substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, that is, those represented by Formula XXI; those wherein R_3 is hydrogen and R_4 is Formula II, that is, those represented by Formula XIV; and those wherein R_3 and R_4 cooperatively form Formula IV, VI, VII, VIII or IX, that is, those represented by Formula XXII:



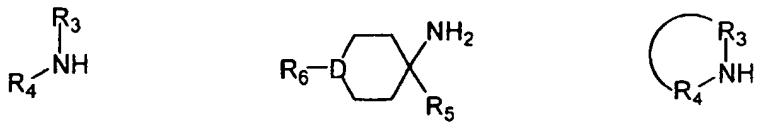
XXI XXII XIV

(wherein D, X, Y, R_3, R_4, R_5 and R_6 represent the same meanings as described above) may be produced by reacting Formula XV:



XV

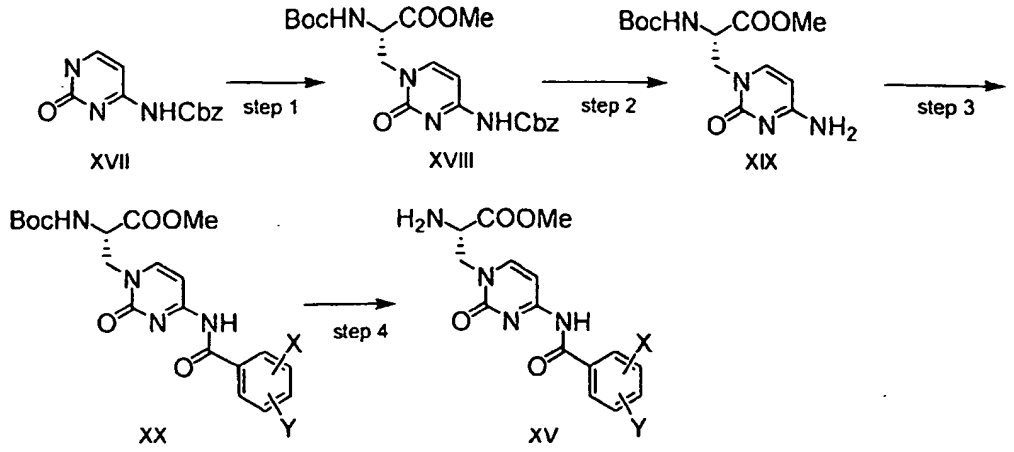
(wherein X and Y represent the same meanings as described above) with p-nitrophenyl chloroformate in a solvent such as dichloromethane, dimethoxyethane or acetonitrile, in the presence of sodium hydrogen carbonate in an amount of about 1 to 4 equivalents with respect to Formula XV; and then reacting the resultant with Formula XXIII, XXIV or XXV in the presence of a tertiary amine such as triethylamine or diisopropylamine in an amount of about 1 to 4 equivalents with respect to Formula XV. Alternatively, they may be produced by reacting Formula XV with Formula XXIII, XXIV or XXV in the presence of a tertiary amine such as triethylamine or diisopropylamine in an amount of about 1 to 4 equivalents with respect to Formula XXIII, XXIV or XXV and treating the mixture with diphosgene, triphosgene or carbozylimidazole in an amount of about 0.5 to 2 equivalents with respect to Formula XXIII, XXIV or XXV:



XXIII XXIV XXV

(wherein X, Y, R_3, R_4, R_5 and R_6 represent the same meanings as described above), and then hydrolyzing the ester group by aqueous sodium hydroxide solution or the like in an alcoholic solvent such as methanol. In the reaction using p-nitrophenyl chloroformate, the mixing ratio between Formula XV and Formula XXIII, XXIV or XXV is not restricted, and usually about 1:1 to 1:2, and the reaction may be carried out usually at a temperature from about 0°C to room temperature for about 1 hour to 24 hours. The hydrolysis by the base such as aqueous sodium hydroxide solution may be carried out usually at a temperature from 0°C to room temperature for about 1 hour to 24 hours, and the amount of the base to be added may be usually about 1 to 4 equivalents with respect to Formula XV, although the reaction conditions are not restricted to those mentioned above.

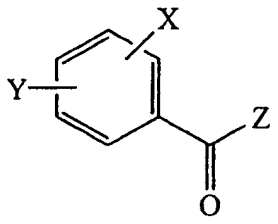
[0029] Formula XV may be produced by the steps below.



[0030] Step 1 may be carried out by reacting N-(2-oxohydropyrimidine-4-yl)(phenylmethoxy)carboxamide Formula XVII and (t-butoxy)-N-(2-oxooxetane-3-yl) carboxamide usually at about 0°C to 50°C for about 1 to 24 hours in a solvent such as tetrahydrofuran or dimethylformamide, and then esterifying the product. As the base, usually, sodium hydride, potassium t-butoxide or the like may be used, but other bases may also be used. The mixing ratio among Formula XVII, (t-butoxy)-N-(2-oxooxetane-3-yl) carboxamide and the base is not restricted, and usually about 1:1:1 to 1:2:2. The esterification may be attained by various methods including those using trimethylsillyldiazometane/methanol, thionyl chloride/methanol or methyl iodide-potassium carbonate/acetone, but the esterification method is not restricted thereto.

[0031] Step 2 is the step for removing benzyloxycarbonyl group (referred to as "Cbz" for short) which is a protective group on the nitrogen atom. This step may be attained by hydrogenating the reactant using a catalytic amount of a palladium catalyst such as palladium/carbon or palladium hydroxide, or using a platinum catalyst such as platinum dioxide in an alcoholic solvent such as methanol or ethanol, or in a polar solvent such as ethyl acetate, tetrahydrofuran or dioxane. The reaction temperature is not restricted, and usually a temperature of about 10 to 30°C is appropriate. The reaction time is not restricted and is appropriately selected depending on the reaction temperature. Usually the reaction time may be about 1 to 20 hours.

[0032] Step 3 is the step for reacting Formula XIX and Formula XVI to produce Formula XX. In cases where the symbol Z in Formula XVI is chloro or bromo, the step may be carried out by reacting Formula XIX and Formula XVI in a solvent such as tetrahydrofuran, dimethylformamide, chloroform or dichloromethane, in the presence of a tertiary amine such as pyridine, triethylamine or diisopropylamine, usually at about 0°C to 60°C for about 1 hour to 24 hours.



XVI

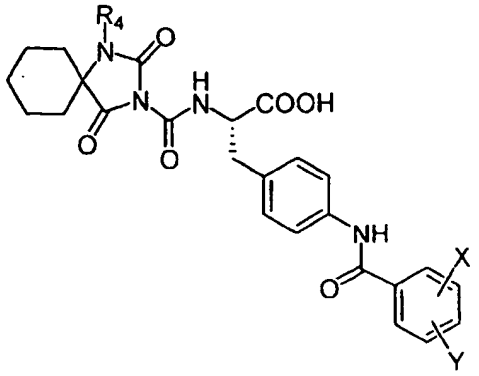
(wherein X and Y represent the same meanings as described above, and Z represents chloro, bromo or hydroxyl)

[0033] The mixing ratio of Formula XIX to XVI is not restricted, and is usually about 1:1 to 1:2. The amount of the tertiary amine to be added is not restricted, and usually about 1 to 4 equivalents with respect to Formula XVI. In cases where Z in Formula XVI is hydroxyl, usually, a condensing agent such as dicyclohexylcarbodiimide (DCC), benzotriazole-1-yloxytris(dicyclopentylamino)phosphoniumhexafluoro phosphite salt (PyBOP), benzotriazole-1-yloxytris (dimethylamino)phosphoniumhexafluoro phosphite salt (BOP), diphenylphosphoryl azide (DPPA) or 1-ethyl-3-[3-(dimethylamino))propyl]carbodiimide (WSC) is used in a solvent such as tetrahydrofuran, dimethylformamide, chloroform or dichloromethane in the presence of a tertiary amine such as triethylamine, diisopropylamine, N-methylmorpholine or N-methylpiperidine. The amount of such a condensing agent to be added is not restricted, and usually about 1 to 3 equivalents with respect to Formula XVI. Addition of an additive such as 1-hydroxybenzotriazole (HOBT)

may be advantageous in the proceeding of the reaction in some cases.

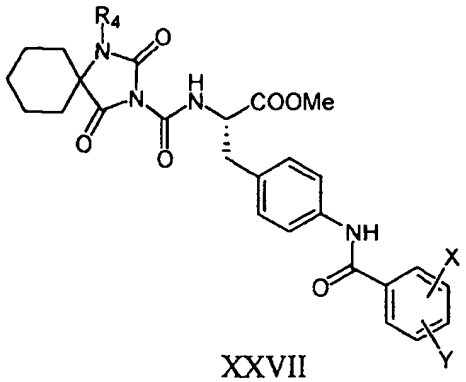
[0034] Step 4 is the step of removing t-butoxycarbonyl group (referred to as "Boc" for short) on the nitrogen atom. This step may be carried out by usually using trifluoroacetic acid, hydrochloric acid, hydrobromic acid or the like in a halogen-containing solvent such as chloroform or dichloromethane. Alternatively, this step may be carried out by using trifluoroacetic acid alone. The reaction temperature is not restricted, and usually a temperature between 0°C and room temperature is selected. The reaction time may be appropriately selected depending on the reaction temperature and the like, and usually, the reaction time may be about 1 to 24 hours.

[0035] Among the compounds represented by Formula I wherein l=0, m=1, R_1 is hydrogen, A is a nitrogen atom, R_2 and R_3 cooperatively form Formula III, A is Formula XI, B is amide, C is Formula XIII, and G does not exist, that is, those represented by Formula XXVI:



XXVI

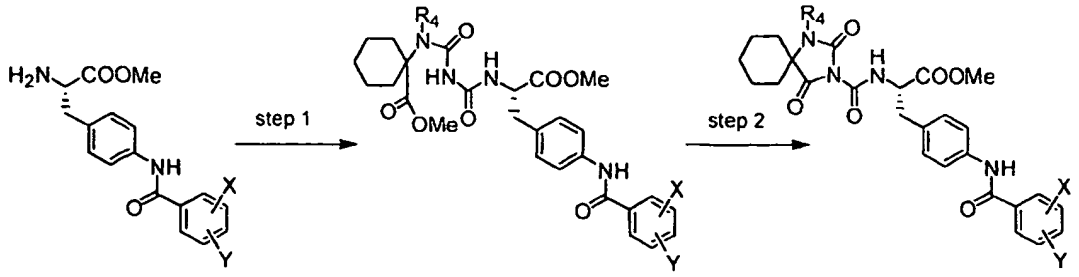
(wherein X, Y and R_4 represent the same meanings as described above) may be produced by hydrolyzing Formula XXVII



XXVII

(wherein X, Y and R_4 represent the same meanings as described above) by aqueous sodium hydroxide solution or the like, in an alcoholic solvent such as methanol. The hydrolysis by a base such as aqueous sodium hydroxide solution may be attained, although not restricted, at a temperature of about 0°C to room temperature for about 1 to 24 hours. The amount of the base to be added is usually about 1 to 4 equivalents.

[0036] Formula XXVII may be carried out by the following steps.

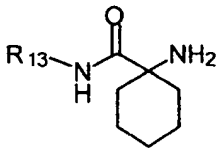


XV XXVIII XXVII

[0037] Step 1 is the step of treating methyl 1-aminocyclohexanecarboxylate with di-t-butyl dicarbonate and dimethylaminopyridine in a solvent such as acetonitrile and then reacting the reaction product with Formula XV to obtain Formula XXVIII. The amounts of the di-t-butyldicarbonate and dimethylaminopyridine are not restricted, and usually about 1 to 3 equivalents, and 0.2 to 1 equivalent, respectively. The reaction temperature and the reaction time are not restricted, and may be about 0°C to room temperature for about 1 to 24 hours. This step may also be carried out under the same conditions as employed in the reaction between Formula XV and Formula XIII, XXIV or XXV.

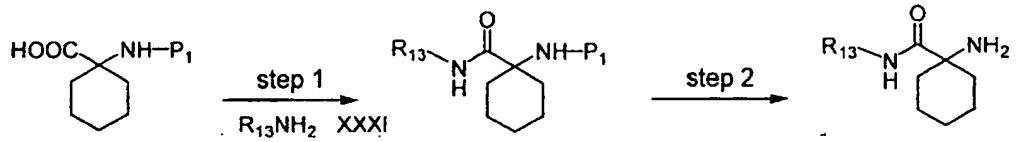
[0038] Step 2 is the step of obtaining Formula XXVII using a base such as sodium hydride or potassium t-butoxide in an alcoholic solvent such as methanol, at about 0°C to room temperature. The amount of the base to be added is not restricted, and may be usually about 1 to 3 equivalents. The reaction time is not restricted, and may be usually about 1 to 24 hours.

[0039] Among the compounds represented by Formula XXIV, those wherein D is a carbon atom, R_6 is a hydrogen atom, R_5 is $-C(O)NHR_{13}$, R_{13} is C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, or phenyl substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, that is, those represented by Formula XXIX



XXIX

(wherein R_{13} represents the same meanings as described above) may be produced by the following steps.



XXX XXXII XXIX

(wherein P_1 represents a protective group and R_{13} represents the same meanings as described above)

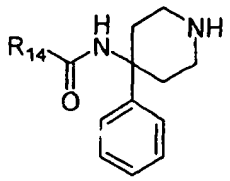
[0040] In Formula XXX, P_1 represents a protective group of the nitrogen atom. The protective group and the method for introducing the protective group are described in, for example, Green and Wuts, "Protective Group in Organic Synthesis" (3rd Edition). The protective groups may be appropriately used in accordance with the reaction conditions described therein.

[0041] Step 1 may be attained by reacting Formula XXX and Formula XXXI in a solvent such as tetrahydrofuran, dimethylformamide or dichloromethane, in the presence of a tertiary amine such as triethylamine, diisopropylamine, morpholine or N-methylpiperidine. The reaction between Formula XXX and Formula XXXI may be usually carried out, although not restricted, at about 0°C to room temperature for about 1 hour to 24 hours. The mixing ratio of Formula XXX to Formula XXXI is not restricted, and may usually be about 1:1 to 1:2. The amount of the tertiary amine to be added is not restricted, and may usually be about 1 to 4 equivalents with respect to Formula XXX. Usually, as the

condensing agent, dicyclohexylcarbodiimide (DCC), benzotriazole-1-yloxytris(dicyclopentylamino)phosphoniumhexafluoro phosphite salt (PyBOP), benzotriazole-1-yloxytris(dimethylamino)phosphoniumhexafluoro phosphite salt (BOP), diphenylphosphoryl azide (DPPA), 1-ethyl-3-[3-(dimethylamino))propyl]carbodiimide (WSC) or the like is used. The amount of the condensing agent is not restricted, and usually about 1 to 3 equivalents with respect to Formula XXX. Addition of an additive such as 1-hydroxybenzotriazole (HOBT) may be advantageous in the proceeding of the reaction in some cases.

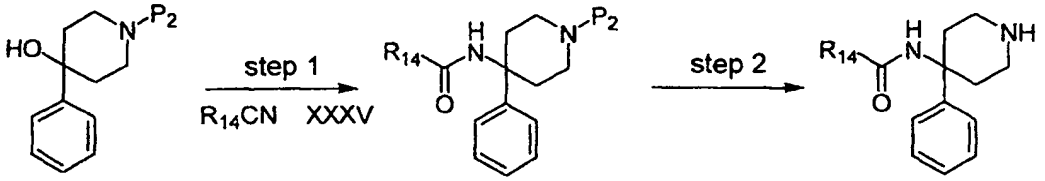
[0042] Step 2 is the step of removing the protective group on the nitrogen atom. The method is described in the above-mentioned "Protective Group in Organic Synthesis" (3rd Edition). The reaction conditions described therein may appropriately be selected.

[0043] Among the compounds represented by Formula XXV, those represented by Formula VI, R_{10} is represented by $R_{14}C(O)NH$-, R_{14} is C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_5-C_7 cycloalkyl, or phenyl substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, that is, those represented by Formula XXXIII:



XXXIII

(wherein R_{14} represents the same meanings as described above) may be produced by the following steps.



XXXIV XXXVI XXXIII

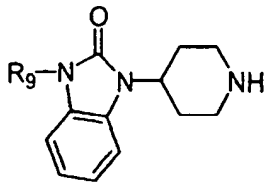
(wherein R_{14} represents the same meanings as described above, P_2 represents a protective group).

[0044] In Formula XXXIV, P_2 represents a protective group of the nitrogen atom. The protective group and the method for introducing the protective group are described in the above-mentioned "Protective Group in Organic Synthesis" (3rd Edition). The protective groups may be appropriately used in accordance with the reaction conditions described therein.

[0045] Step 1 may be attained by reacting Formula XXXIV and Formula XXXV in the presence of acetic acid, sulfuric acid or Lewis acid for usually 1 to 24 hours. The reaction temperature is not restricted and usually from ice to about 100°C. The mixing ratio of Formula XXXIV to Formula XXXV is not restricted and usually about 1:1 to 1:10. The equivalent of the acid is not restricted, and usually an excess amount with respect to Formula XXXIV is used.

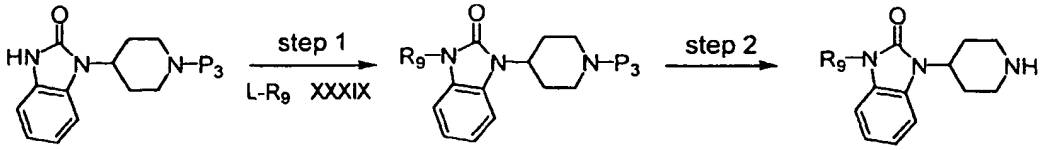
[0046] Step 2 may be appropriately carried out in accordance with the reaction conditions described in the above-mentioned "Protective Group in Organic Synthesis" (3rd Edition).

[0047] Among the compounds represented by Formula XXV, those represented by Formula IV, wherein E is a carbon atom, R_7 is a hydrogen atom and R_8 is Formula V, that is, those represented by Formula XXXVII:



XXXVII

(wherein R_9 represents the same meanings as described above) may be produced by the following steps.



XXXVIII XXXX XXXVII

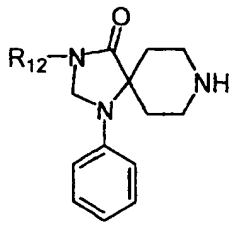
(wherein R_9 represents the same meanings as described above, L represents a leaving group such as halogen, methanesulfonyloxy or p-toluenesulfonyloxy, P_3 represents a protective group).

[0048] In Formula XXXVIII, P_3 represents a protective group of the nitrogen atom. The protective group and the method for introducing the protective group are described in the above-mentioned "Protective Group in Organic Synthesis" (3rd Edition). The protective groups may be appropriately used in accordance with the reaction conditions described therein.

[0049] Step 1 may be attained by reacting Formula XXXVIII and Formula XXXIX for about 1 to 24 hours in a solvent such as dimethylformamide, dimethylacetylamide or acetonitrile, in the presence of a base such as potassium carbonate, potassium hydroxide, diisopropylamine or triethylamine. The mixing ratio of Formula XXXVIII to Formula XXXIX is not restricted, and is usually about 1:1 to 1:3. The equivalent of the base is not restricted, and is usually 1 to 4 equivalents. The reaction temperature is not restricted, and may be usually about room temperature to reflux.

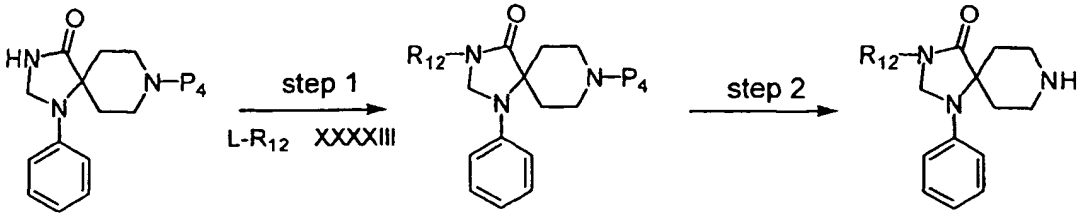
[0050] Step 2 may be appropriately carried out in accordance with the reaction conditions described in the above-mentioned "Protective Group in Organic Synthesis" (3rd Edition).

[0051] Among the compounds represented by Formula XXV, Formula XXXXI:



XXXXI

(wherein R_{12} represents the same meanings as described above) represented by Formula IX may be produced by the following steps.



XXXXII XXXXIV XXXXI

(wherein R_{12} represents the same meanings as described above, L represents a leaving group such as halogen, methanesulfonyloxy or p-toluenesulfonyloxy, P_4 represents a protective group).

[0052] In Formula XXXXII, P_4 represents a protective group of the nitrogen atom. The protective group and the method for introducing the protective group are described in the above-mentioned "Protective Group in Organic Synthesis" (3rd Edition). The protective groups may be appropriately used in accordance with the reaction conditions described therein.

[0053] Step 1 may be carried out in the same manner as in step 1 in the production process of Formula XXXVII.

[0054] Step 2 may be appropriately carried out in accordance with the reaction conditions described in the above-mentioned "Protective Group in Organic Synthesis" (3rd Edition).

[0055] Among the compounds represented by Formula XXV, Formula XXXXV represented by Formula VII, and Formula XXXXVI represented by Formula VIII, may be produced by the methods described in Tetrahedoron, 53 , 10983 , 1997 and Chem.Pharm.Bull. ,46, 242, 1998, Chem.Pharm.Bull. ,46, 1538, 1998, respectively.

XXXXV XXXXVI

(wherein F and R_{11} represent the same meanings as described above).

[0056] The reaction products obtained by the above-described processes may be isolated and purified in the form of a free compound, a salt or a solvate such as hydrate. The salt may be produced by a usual salt-producing treatment.

[0057] Isolation and purification may be carried out by ordinary chemical processes such as extraction, condensation, evaporation, crystallization, filtration, recrystallization and various column chromatography.

[0058] Various isomers may be isolated by conventional methods utilizing the differences in the physicochemical properties between the isomers. Optical isomers may be separated by a general optical resolution method such as fractional crystallization or chromatography. Optical isomers may also be produced by an appropriate optically active compound as the starting material.

[0059] In cases where the novel urea derivatives used in the present invention have one or more asymmetric carbon atoms, there exist racemic compounds, diasteromers and optical isomers. In the present invention, any of these may be used.

[0060] Examples of the pharmaceutically acceptable salts of the compounds represented by Formula I include inorganic salts such as ammonium salt, alkaline metal salts (e.g., sodium salt and potassium salt), alkaline earth metal salts (e.g., calcium salt and magnesium salt); organic salts such as dicyclohexylamine salt, N-methyl-D-glucamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, diisopropanolamine salt and tris(hydroxymethyl) aminemethane salt; and lysine- and arginate-addition salts.

[0061] The inhibitory activity of the compound according to the present invention against the adhesion of VLA-4 may be determined by using an adhesion-measuring system in which the adhesion between VLA-4-expressing cells such as Ramos cells or Jurkat cells and fibronectin or fibronectin fragment such as a peptide containing CS-1 sequence (Gly Pro Glu Ile Leu Asp Val Pro Ser Thr) (hereinafter referred to as "CS-1 peptide"), immobilized on an immunoplate is measured. Alternatively, a binding-measuring system in which the adhesion between VLA-4 protein and fibronectin or fibronectin fragment such as CS-1 peptide, immobilized on an immunoplate may be used. In the present invention, it is preferred to evaluate the inhibitory activity of a compound using a binding-measuring system in which adhesion

between a chimera protein of VLA-4-immunoglobulin (VLA-4-IgG chimera protein) and CS-1 peptide (Japanese Patent Application No. H9-234544), but the method is not restricted thereto. The "VLA-4-IgG chimera protein" herein means the heterodimer complex of the chimera protein between α4 of VLA-4 and immunoglobulin (hereinafter referred to as "VLAα4-IgG chimera protein") and a chimera protein between β1 of VLA-4 and immunoglobulin (hereinafter referred to as "VLAβ1-IgG chimera protein"). As the immunoglobulin, although heavy chain or light chain of IgG, IgM or the like may be used, IgG 1 heavy chain is used in the present invention. When testing the inhibitory effect of a compound, it is preferred to mix VLA-4-IgG chimera protein and the test compound previously.

[0062] Since the compounds according to the present invention have inhibitory activities against adhesion of VLA-4, and so inhibit accumulation of leukocytes at the inflammatory site, they may be used as therapeutic drugs against chronic inflammatory diseases. Examples of the chronic inflammatory diseases include allergic inflammatory diseases such as bronchial asthma, atopic dermatitis and allergic rhinitis, hepatitis, nephritis, autoimmune diseases such as chronic rheumatoid arthritis and multiple sclerosis, graft rejections after organ transplantation, type I diabetes, Crohn's disease and ulcerative colitis. In addition to these, they may be used as therapeutic drugs for the prevention of post-operative restenosis, arteriosclerosis and the like.

[0063] When using the compound of the present invention as a therapeutic drug against the above-mentioned diseases, the compound represented by Formula I or a base addition salt thereof may be administered as it is in the form of powder, or may be administered as a medical composition in the form of an appropriate formulation, orally or parenterally (e.g., percutaneous administration, intravenous administration, rectal administration and inhalation) to mammals.

[0064] Examples of the formulation for administration include tablets, powders, balls, capsules, granules, syrups, liquids, injection solutions, emulsions, suspensions and suppositories. These formulations may be prepared by the methods which *per se* are known, and contain various carriers usually used in the field of formulation. Examples thereof include vehicles, lubricants, binders and disintegrators for solid formulations; and solvents, solubilizers, suspending agents and soothing agents for liquid formulations. Additives such as antiseptics, antioxidants, coloring agents, sweeteners, absorbents, and wetting agents may be used.

[0065] Examples of the vehicles include lactose, D-mannitol, starch, sucrose, corn starch, crystalline cellulose and light anhydrous silicic acid. Examples of the lubricants include magnesium stearate, calcium stearate, talc and colloidal silica. Examples of the binders include crystalline cellulose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinylpyrrolidone, starch, sucrose, gelatin, methyl cellulose and sodium carboxymethyl cellulose. Examples of the disintegrators include starch, carboxymethyl cellulose, calcium carboxymethyl cellulose, cross carmelose sodium, sodium carboxymethyl starch and L-hydroxypropyl cellulose. Examples of the solvents include water for injection, alcohol, propylene glycol, Macrogol, sesame oil and corn oil. Examples of the solubilizers include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, cholesterol, triethanolamine, sodium carbonate and sodium citrate. Examples of the suspending agents include surfactants such as stearyl triethanolamine, sodium lauryl sulfate, laurylamino propionate, lecithin, benzalkonium chloride, benzethonium chloride and glycerin monostearate, and hydrophilic macromolecules such as polyvinyl alcohol, polyvinyl pyrrolidone, methyl cellulose, hydroxymethyl cellulose, hydroxyethyl cellulose and hydroxypropyl cellulose. Examples of the isotonic agents include glucose, sodium chloride, D-sorbitol and D-mannitol. Examples of the buffering agents include buffering solutions containing a phosphoric acid salt, acetic acid salt, carbonic acid salt or citric acid salt. An example of the soothing agents is benzylalcohol. Examples of the antiseptics include p-oxybenzoic acid esters, chlorobutanol, benzylalcohol, phenetyl alcohol, dehydroacetic acid and sorbic acid. Examples of the antioxidants include sulfurous acid salts and ascorbic acid.

[0066] The effective dose and the number of-times of administration of the compounds represented by Formula I and pharmaceutically acceptable salts thereof differ depending on the administration form, age and bodyweight of the patient, the type and severity of the disease to be treated, and usually, 1 to 1000 mg, preferably 1 to 300 mg of the compound may be administered once or in several times per day per adult.

[0067] The above-mentioned formulations may contain one or more other effective components for therapy of other disease(s). Examples thereof include steroid drugs, nonsteroidal anti-inflammatory drug, lipoxygenase inhibitors, leucotriene inhibitors, bronchodilators, thromboxane synthesis inhibitors, thromboxane antagonists, histamine antagonists, histamine release inhibitors, platelet activating factor (PAF) inhibitors, serotonin antagonist, adenosine receptor antagonists, adrenalin β receptor stimulators, immunosuppressors and immunomodulators.

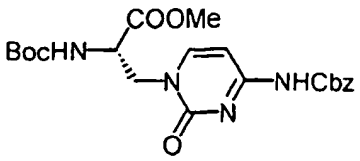
Examples

[0068] The effect of the present invention will now be described concretely by way of examples thereof. It should be noted that the present invention is not restricted to the examples.

Example 1

Methyl 2-((t-butoxy)carbonylamino)-3 -(2-oxo-4-((phenylmethoxy)carbonylamino)hydropyrimidinyl)propionate (1)

[0069]



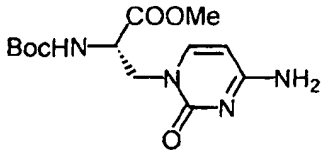
(1)

[0070] Under argon atmosphere, 4.86 g (19.8 mmol) of N-(2-oxohydropyrimidine-4-yl)(phenylmethoxy)carboxamide was suspended in 50 ml of DMF, and 0.76 g (19 mmol) of sodium hydride was added to the mixture while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 40 minutes. To the reaction mixture, 3.37 g (18 mmol) of (t-butoxy)-N-(2-oxooxetane-3-yl)carboxamide in 10 ml of DMF was added while cooling the reaction mixture in ice, followed by stirring the resulting mixture at room temperature overnight. Water was added to the reaction mixture, and precipitated solids were removed by filtration. To the filtrate, 1N hydrochloric acid was added and the resultant was extracted with chloroform. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in 20 ml of methanol, and 20 ml of trimethylsillyldiazomethane was added while cooling the mixture in ice, followed by stirring the resulting mixture for 30 minutes. The reaction solution was concentrated and the residue was purified by silica gel column chromatography (hexane: ethyl acetate = 1:1) to obtain 4.02 g of methyl 2-((t-butoxy)carbonylamino)-3 -(2-oxo-4-((phenylmethoxy)carbonylamino)hydropyrimidinyl)propionate (yield: 50%). LR-MS(m/z):446(M^+)
NMR(300MHz,CD_3OD, δ ppm):3.75(3H,s),3.79-3.93(1H,m),4.46-455(1H,m),4.62-4.68(1H,m),5.21(2H,s),7.07-7.28(2H,m),7.32-7.43(4H,m),7.80(1H,m)

Example 2

Methyl 3-(4-amino-2-oxohydropyrimidinyl)-2-((t-butoxy)carbonylamino) propionate (2)

[0071]



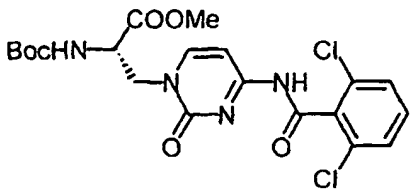
(2)

[0072] Under argon atmosphere, 4.02 g (9.0 mmol) of methyl 2-((t-butoxy)carbonylamino)-3-(2-oxo-4-((phenylmethoxy)carbonylamino)hydropyrimidinyl)propionate was dissolved in 20 ml of methanol and 400 mg of 10% palladium/carbon was added thereto. The mixture was subjected to hydrogen replacement and stirred at room temperature for 1 hour. The reaction mixture was filtered through Celite and the filtrate was concentrated. The residue was purified by silica gel column chromatography (chloroform:methanol = 4:1) to obtain 2.53 g of methyl 3-(4-amino-2-oxohydropyrimidinyl)-2-((t-butoxy)carbonylamino) propionate (yield: 90%). LR-MS(m/z):312(M^+)
NMR(300MHz,CD_3OD, δ ppm): 1.39(9H,s),2.31(2H,s),3.73(3H,s),3.75-3.82(1H,m), 4.33-4.40(1H,m), 4.53-4.60(1H,m),5.80(1H,m),7.05-7.21(1H,m),7.4(1H,m)

Example 3

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((t-butoxy)carbonylamino) propionate (3)

[0073]



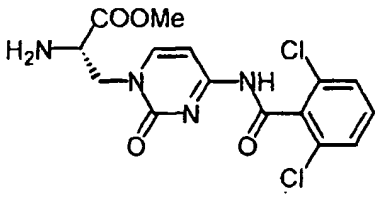
(3)

[0074] In 15 ml of pyridine and 10 ml of dichloromethane, 2.96 g (9.48 mmol) of methyl 3-(4-amino-2-oxohydropyrimidinyl)-2-((t-butoxy)carbonylamino) propionate was dissolved, and 2.7 ml (19.0 mmol) of dichlorobenzoyl chloride was added, followed by stirring the resulting mixture at 50°C for 2 hours. Methanol was added to the reaction solution and the mixture was concentrated. To the residue, 3N hydrochloric acid was added and the resultant was extracted with chloroform. The organic phase was washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (chloroform:methanol = 20:1) to obtain 3.35 g of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((t-butoxy)carbonylamino) propionate (yield: 73%).
LR-MS(m/z):484(M^+)
IR(KBr):3442,3222,2962,1701,1627,1562,1492,1435,1369,1334,1303,1250,1162, 788cm-1
NMR(300MHz,CD_3OD, δ ppm):1.38(9H,s),3.77(3H,s),3.83-3.94(1H,m), 4.55-4.63(1H,m), 4.68-4.77(1H,m), 7.41-7.55 (4H,m),7.93-7.98(1H,m)

Example 4

Methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate (4)

[0075]



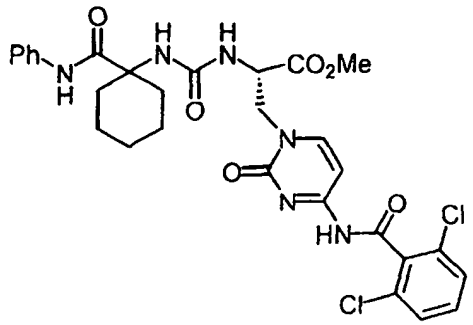
(4)

[0076] Under argon atmosphere, 202 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((t-butoxy)carbonylamino) propionate was suspended in 9 ml of dichloromethane, and I ml of trifluoroacetic acid was added thereto while cooling the mixture in ice. The reaction solution was stirred at room temperature for 3 hours and concentrated. The residue was dissolved in ethyl acetate and saturated aqueous sodium hydrogen carbonate solution was added to the mixture while cooling the mixture in ice, followed by extraction of the resulting mixture with ethyl acetate. The organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated to obtain 156 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate (97%).
LR-MS(m/z):385(M^++H)
NMR(300MHz,CD_3OD,δ ppm):3.74(3H,S),3.91-4.02(2H,m),4.23-4.30(1H,m),7.38-7.57(3H,m),8.03-8.05(1H,m)

Example 7

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((((N-phenylcarbamoyl)cyclohexyl)amino) carbonylamino) propionate (7)

[0077]



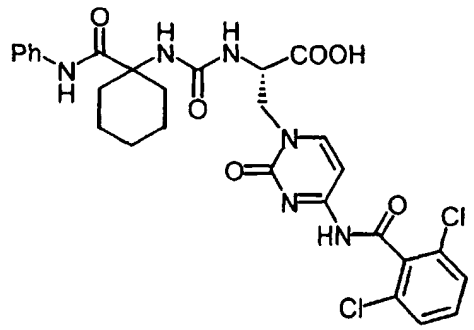
(7)

[0078] Under argon atmosphere, to a solution of 78 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate in 5 ml of acetonitrile and 5 ml of dichloromethane, 90 mg of sodium hydrogen carbonate and 47 mg of chloroformic acid p-nitrophenyl ester were added, and the resulting mixture was stirred at room temperature for 2 hours. To the reaction mixture, a solution of 68 mg of (aminocyclohexyl)-N-benzamide and 0.1 ml of triethylamine in 3 ml of acetonitrile was added and the resulting mixture was stirred for 44 hours. To the reaction mixture, IN hydrochloric acid was added and the mixture was extracted with chloroform. Organic phases were combined, washed with saturated aqueous sodium hydrogen carbonate solution and with saturated saline, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from ethyl acetate to obtain 56 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((((N-phenylcarbamoyl)cyclohexyl)amino) carbonylamino) propionate (yield: 45%).
mp.248°C
LR-MS(m/z):629(M^+) IR(KBr):3393,2936,1713,1654,1628,1558,1493,1437,1369,1342,1304,1246,792, 757cm^{-1}
NMR(300MHz,DMSO-d_6, δ ppm):1.20-1.70(8H,m), 1.90-2.06(2H,m), 3.64(3H,s), 4.04(1H,m), 4.28(1H,m), 4.54(1H, m), 6.39(1H,s), 6.80(1H,d,J=8.2Hz), 6.99(1H,t,J=7.4Hz), 7.25(3H,t,J=8.0Hz), 7.45-7.61(5H,m), 7.89(1H,bd,J=7.5Hz), 9.34(1H,bs), 11.64(1H,bs)

Example 8

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((((N-phenylcarbamoyl)cyclohexyl)amino) carbonylamino)propanoic acid (8)

[0079]



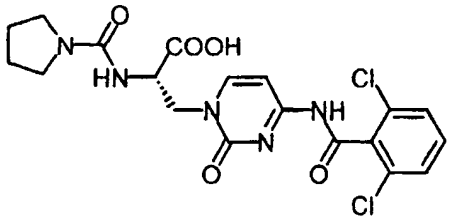
(8)

[0080] In 10 ml of methanol and 10 ml of tetrahydrofuran, 52 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((((N-phenylcarbamoyl)cyclohexyl)amino)carbonylamino) propionate was dissolved, and 1 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the mixture at room temperature for 2 hours. The reaction solution was concentrated and 1N hydrochloric acid was added to the residue, followed by recovery of the precipitated crystals to obtain 29 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((((N-phenylcarbamoyl)cyclohexyl)amino)carbonylamino)propanoic acid (yield: 55%). mp.193-195°C
LR-MS(m/z):615(M^+)
IR(KBr):3368,2938.2860,1719,1668,1656,1629,1599,1561,1492,1433,1367,1312,13
03,1244,1196,1158,1133,788,756,694cm^{-1}
NMR(300MHz,DMSO-d_6, δ ppm): 1.15-1.70(8H,m), 1.89-1.96(2H,m), 3.96(1H,dd,J=8.2, 13.0Hz), 4.34(1H,dd,J=4.4, 13.0Hz), 4.49(1H,m), 6.37(1H,s), 6.71(1H,d,J=8.2Hz), 6.98(1H,t,J=7.4Hz), 7.19-7.29(3H,m), 7.44-7.59(5H,m), 7.90 (1H,d,J=7.4Hz), 9.34(1H,bs), 11.62(1H,bs)

Example 9

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(pyrrolidinylcarbonylamino)propanoic acid (9)

[0081]



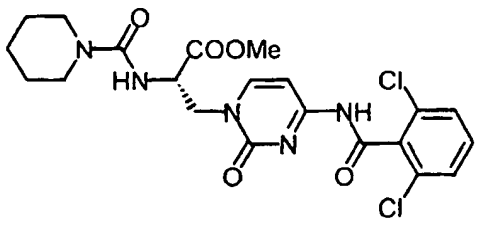
(9)

[0082] Under argon atmosphere, to a solution of 60 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate in 4 ml of acetonitrile, 51.4 mg of saturated sodium hydrogen carbonate and 41.4 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, and the resulting mixture was stirred at room temperature for 18 hours. To the reaction mixture, 16.3 μl of pyrrolidine and 27 μl of triethylamine were added and the resulting mixture was stirred at room temperature for 2 hours. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in 3 ml of methanol and 0.3 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 20 hours. To the reaction solution, 1N hydrochloric acid was added and the mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (chloroform:methanol = 20:1) to obtain 14 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(pyrrolidinylcarbonylamino)propanoic acid (yield: 23%) LR-MS(m/z):466(M^+-H)
IR(KBr):3423, 2925, 1719, 1627, 1561, 1493, 1432, 1365, 1306, 1246cm^{-1}
NMR(300MHz,$CDCl_3$, δ ppm): 1.80-2.00 (m, 4H), 3.22-3.40 (m, 4H), 4.39 (dd, J=14.0, 8.8 Hz, 1H), 4.48 (dd, J=14.0, 4.1 Hz, 1H), 4.62 (dd, J=8.8, 4.1 Hz, 1H),6.96 (br s, 1H), 7.30-7.40 (m, 3H), 7.63 (d, J=7.4 Hz, 1H), 8.11 (d, J=7.4 Hz, 1H). HR-MS:$C_{19}H_{19}Cl_2N_5O_5$ Calcd.: 466.0685, Found: 466.0639
$[\alpha]^{20}_D$:-101.6° (c=0.70,MeOH)

Example 10

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(piperidylcarbonylamino) propionate (10)

[0083]



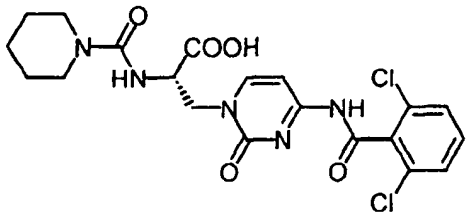
(10)

[0084] Under argon atmosphere, 61 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 2 ml of acetonitrile and 3 ml of dichloromethane, and 22 mg of saturated sodium hydrogen carbonate and 35 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 2 hours. To the reaction mixture, 11 μl of piperidine and 56 μl of triethylamine were added and the resulting mixture was stirred at room temperature for 15 hours. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 20:1) to obtain 60 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(piperidylcarbonylamino) propionate (yield: 76%).
LR-MS(m/z):495(M^+)
IR(KBr):3372,2937,2855,1716,1658,1627,1562,1494,1433,1368,1305,1247,1131, 790cm^{-1}
NMR(300MHz,$CDCl_3$,δ ppm): 1.42-1.66(6H,m),3.23-3.38(4H,m),3.78(3H,s),4.28-4.42(2H,m),4.70-4.78(1H,m), 6.10-6.18(1H,m),7.27-7.58(4H,m),7.82-7.91(1H,m), 9.38(1H,brs)
$[\alpha]_D^{20}$: -115.5° (C=0.10, MeOH)

Example 11

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(piperidylcarbonylamino) propanoic acid (11)

[0085]



(11)

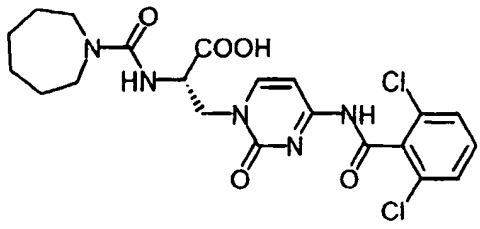
In 2 ml of methanol, 55 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(piperidylcarbonylamino) propionate was added and 0.5 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the mixture at room temperature for 12 hours. To the reaction solution, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/n-hexane to obtain 46.4 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(piperidylcarbonylamino) propanoic acid (yield: 87%)
LR-MS(m/z):481(M^+-H)
IR(KBr):3402,2938,2856,1715,1627,1494,1431,1367,1306,1250,1133,902,791cm^{-1} NMR(300MHz,$CDCl_3$, δ ppm): 1.50-1.70(6H,m),3.22-3.46(4H,m),4.31-4.53(2H,m),4.60-4.70(1 H,m),7.01-7.42(5H,m),7.60-7.71(1H,m),8.08(1H,brs)
HR-MS:$C_{20}H_{20}Cl_2N_5O_5$ Calcd.: 480.0841, Found: 480.0863

$[\alpha]_D^{20}$: -30.4° (C=0.04, MeOH)

Example 12

2-(azaperhydroepinylcarbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid (12)

[0086]



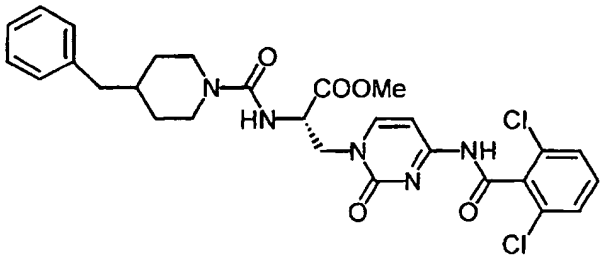
(12)

[0087] Under argon atmosphere, to a solution of 50 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate in 4 ml of acetonitrile, 17.4 mg of saturated sodium hydrogen carbonate and 32 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, and the resulting mixture was stirred at room temperature for 1 hour. To the reaction mixture, 28 µl of hexamethyleneimine and 100 µl of triethylamine were added, and the mixture was stirred at room temperature for 15 hours. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in 3 ml of methanol, and 0.3 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 20 hours. To the reaction solution, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 20:1) to obtain 26.2 mg of 2-(azaperhydroepinylcarbonylamino)-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)propanoic acid (yield: 39%). LR-MS(m/z):494(M^+-H)
IR(KBr):3346, 2926, 1727, 1703, 1647, 1562, 1529, 1488, 1434, 1371, 1314, 1253cm^{-1}
NMR(300MHz,CD_3OD, δ ppm):1.50-1.80 (m, 8H), 3.35-3.45 (m, 4H), 4.13 (dd, J=13.5, 9.9 Hz, 1H), 4.62-4.80 (m, 2H), 7.50-7.60 (m, 4H), 8.03 (d, J=7.2 Hz). HR-MS:$C_{21}H_{22}Cl_2N_5O_5$ Calcd.: 494.0998, Found: 494.1004
$[\alpha]^{20}_D$:-125.0° (c=0.50,MeOH)

Example 13

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-benzylpiperidyl)carbonylamino) propionate (13)

[0088]



(13)

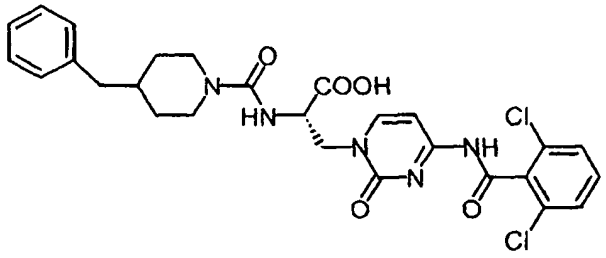
[0089] Under argon atmosphere, 72.0 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyridiminyl) propionate was dissolved in 4 ml of acetonitrile and 4 ml of dichloromethane, and 29 mg of saturated sodium hydrogen carbonate and 30 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture

in ice, followed by stirring the resulting mixture at room temperature for 3 hours. To the reaction mixture, 30 µl of 4-benzylpiperidine and 49 µl of triethylamine were added and the resulting mixture was stirred at room temperature for 19 hours. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 20:1) to obtain 30.5 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-benzylpiperidyl)carbonylamino) propionate (yield: 37%).
LR-MS(m/z):585(M^+) IR(KBr):3341,2924,2850,1716,1658,1628,1562,1493,1433,1368,1304,1246,1055, 966,901,790,701 cm^{-1}
NMR(300MHz,$CDCl_3$, δ ppm):1.07-1.30(2H,m),1.02-1.10(2H,m),1.60-1.82(3H,m),2.50-2.60(2H,m),2.61-2.68(2H,m), 3.78(3H,m),3.83-3.96(2H,m),4.31-4.40(2H,m),4.65-4.76(1H,m),6.05-6.16(1H,m),7.04-7.40(8H,m),7.51(1H,brs), 7.78-7.82(1H,m),9.07(1H,brs)
$[\alpha]_D^{20}$: -117.1° (C=0.08, MeOH)

Example 14

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-benzylpiperidyl)carbonylamino)propanoic acid (14)

[0090]



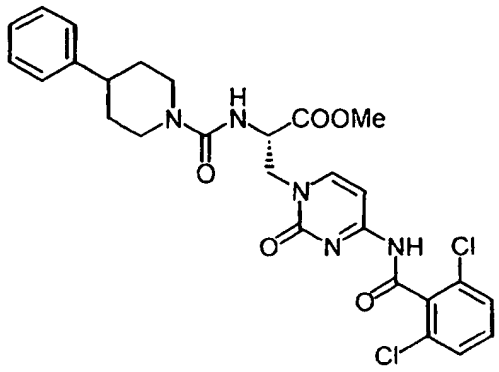
(14)

[0091] In 2 ml of methanol, 26 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-benzylpiperidyl)carbonylamino) propionate was dissolved, and 0.2 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the mixture at room temperature for 3 hours. To the reaction solution, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/n-hexane to obtain 16.6 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-benzylpiperidyl)carbonylamino)propanoic acid (yield: 72%).
LR-MS(m/z):570(M^+-H) IR(KBr):3407,2924,1717,1628,1494,1431,1367,1306,1246,1196,1132,964,901,791,747,701 cm^{-1}
NMR(300MHz,CD_3OD, δ ppm):1.07-1.30(2H,m),1.60-1.80(3H,m),2.51-2.79(4H,m),3.86-3.98(2H,m),4.32-4.50(2H,m),4.54-4.60(1H,m),7.11-7.40(10H,m)7.61(1H,brs),7.87(1H,brs)
HR-MS:$C_{27}H_{26}Cl_2N_5O_5$ Calcd.: 570.1311, Found: 570.1323
$[\alpha]_D^{20}$: -113.5° (C=0.05, MeOH)

Example 15

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-phenylpiperidyl)carbonylamino) propionate (15)

[0092]



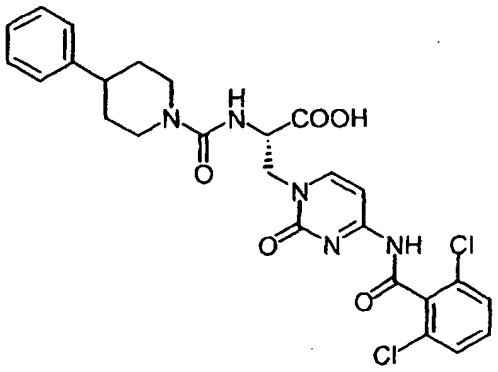
(15)

[0093] Under argon atmosphere, to a solution of 7 mg of triphosgene in 1 ml of dichloromethane, 24.4 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate and 1 ml of a solution of 0.012 ml of diisopropylethylamine in dichloromethane were dropped, and the resulting mixture was stirred at room temperature for 10 minutes. To the reaction mixture, 1 ml of a solution of 10.8 mg of 4-phenylpiperidine and 0.013 ml of diisopropylethylamine in dichloromethane were added, and the resulting reaction mixture was stirred at room temperature for 45 minutes. After concentrating the reaction mixture, 6 ml of 10% aqueous citric acid solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (chloroform/methanol = 30:1) to obtain 22.1 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-phenylpiperidyl)carbonylamino) propionate (yield: 61%).
LR-MS(m/z):571(M^+)
IR(KBr):2937,2850,1741,1716,1657,1626,1561,1493,1432,1369,1305,1243,1131,10 11,985,902,797cm^{-1}
NMR(300MHz,$CDCl_3$, δ ppm):1.52-1.76(2H,m),1.80-1.89(2H,m),2.60-2.73(1 H,m),2.81-2.96(2H,m),3.77(3H,s), 4.01-4.12(2H,m),4.36-4.42(2H,m),4.72-4.80(1H,m),6.21-6.25(1H,m),7.15-7.25(3H,m),7.26-7.39(5H,m),7.56(1H,brs), 7.81-7.87(1 H.m),8.88(1H,brs)
$[\alpha]^{20}_D$:+11.7° (c=0.02,MeOH)

Example 16

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-phenylpiperidyl)carbonylamino)propanoic acid (16)

[0094]



(16)

[0095] In 1.2 ml of methanol, 32.7 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-phenylpiperidyl)carbonylamino) propionate was dissolved, and 0.3 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture overnight at room temperature. To the reaction solution, 4 ml of 0. IN hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from methanol/ether to obtain 18.5 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-phenylpiperidyl)carbonylamino)propanoic acid (yield: 58%).

LR-MS(m/z):558($M+H^+$)

IR(KBr):3402,2934,2852,1723,1651,1634,1562,1491,1431,1368,1305,1241,1192, 1131,984,901,792cm^{-1}

NMR(300MHz,CD_3OD, δ ppm): 1.54-1.70(2H,m),1.73-1.85(2H,m),2.68-2.70(1H,m),2.84-3.00(2H,m),4.05-4.17(3H, m),4.64-4.42(2H,m),4.72-4.82(3H,m),7.12-7.32(5H,m),7.41-7.60(4H,m),7.98-8.02(1H.m)

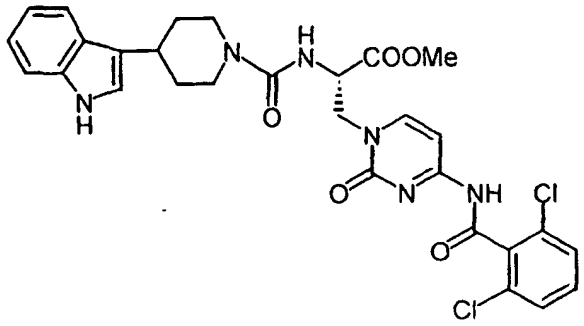
HR-MS:$C_{26}H_{26}Cl_2N_5O_5$

Calcd.: 558.1311, Found: 558.1271

Example 17

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-indol-3-ylpiperidyl)carbonylamino) propionate (17)

[0096]



(17)

[0097] Under argon atmosphere, to a solution of 51.8 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate in 2 ml of acetonitrile and 3 ml of dichloromethane, 18 mg of saturated sodium hydrogen carbonate and 29 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, and the resulting mixture was stirred at room temperature for 7 hours. To the reaction mixture, 4 ml of a solution of 32 mg of 3-(4-piperidyl)indole and 0.46 ml of triethylamine in acetonitrile were added and the resulting mixture was stirred overnight at room temperature. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 30:1) to obtain 72 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-indol-3-ylpiperidyl)carbonylamino) propionate (yield: 91%).

LR-MS(m/z):610(M^+)

IR(KBr):3299,2932,2851,1716,1658,1562,1491,1432,1368,1305,1244,1130,1103,10 03,983,901,788,743cm^{-1}

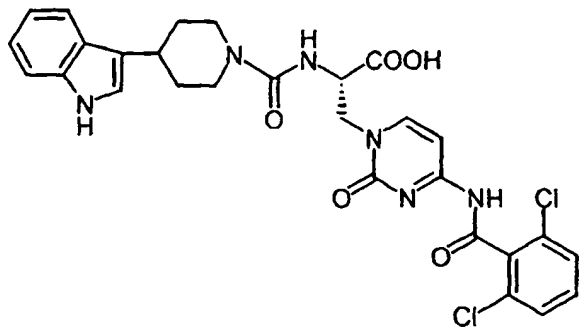
NMR(300MHz,$CDCl_3$, δ ppm):1.33-1.60(2H,m),1.79-2.02(2H,m),2.77-2.99(3H,m),3.76(3H,s),3.81-4.04(2H,m), 4.24-4.39(2H,m),4.79-4.90(1H,m),6.05-6,18(1H,m),6.93(1H,s),7.05-7.39(6H,m),7.42-7.63(2H,m),7.84-7.96(1H,m), 8.60(1H,brs),9.82(1H,brs)

$[\alpha]_D^{20}$: -160.2° (C=0.13, MeOH)

Example 18

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-indol-3-ylpiperidyl)carbonylamino)propanoic acid (18)

[0098]



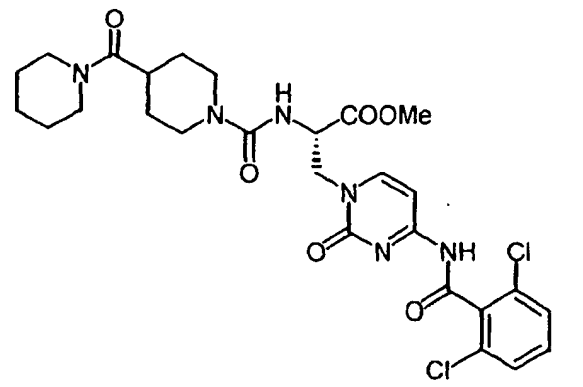
(18)

[0099] In 2 ml of methanol, 52 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-indol-3-ylpiperidyl)carbonylamino) propionate was dissolved, and 0.5 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 1 hour. To the reaction solution, 1N hydrochloric acid and water were added, and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/ether to obtain 14.5 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-indol-3-ylpiperidyl)carbonylamino)propanoic acid (yield: 82%).
LR-MS(m/z):595(M^+-H)
IR(KBr):3405,2934,2853,1717,1627,1563,1492,1431,1366,1305,1245,1195,1131,11 03,984,901,787,744scm^{-1}
NMR(300MHz,CD_3OD δ ppm): 1.57-1.74(2H,m),2.02-2.15(2H,m),2.81-3.10(3H,m),4.02-4.16(2H,m),4.32-4.53(2H,m), 4.56-4.65(1H,m), 6.99(1H,s),7.05-7.21(2H,m),7.32-7.50(4H,m),7.58-7.65(2H,m),7.82-7.90(1H,m)
HR-MS:$C_{28}H_{25}Cl_2N_6O_5$ Calcd.: 595.1263, Found: 595.1249
$[\alpha]_D^{20}$: -56.5° (C=0.04, MeOH)

Example 19

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(cyclohexylcarbonyl)piperidyl) carbonylamino) propionate (19)

[0100]



(19)

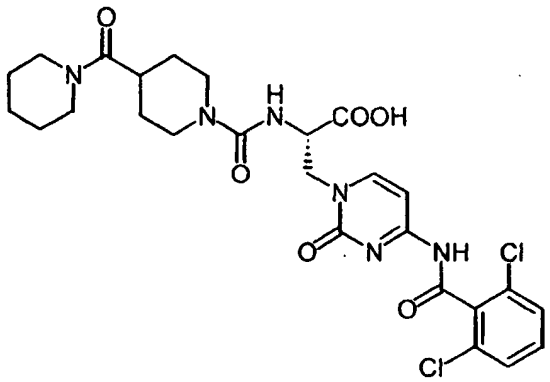
[0101] Under argon atmosphere, to a solution of 60 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate in 4 ml of acetonitrile, 19.7 mg of saturated sodium hydrogen carbonate and 37.7

mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 3 hours. To the reaction mixture, 4 ml of a solution of 42.9 mg of 4-piperidylpiperidyl ketone and 0.11 ml of triethylamine in acetonitrile were added, and the resulting mixture was stirred overnight at room temperature. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (chloroform/methanol = 30:1) to obtain 71.0 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(cyclohexylcarbonyl)piperidyl)carbonylamino) propionate (yield: 75%).
LR-MS(m/z):606(M^+)
IR(KBr):3005,2941,2856,1741,1718,1659,1626,1493,1433,1369,1305,1216cm^{-1}
NMR(300MHz,$CDCl_3$, δ ppm): 1.45-1.92(10H,m),2.60-2.75(1H,m),2.77-2.94(2H,m),3.38-3.51(4H,m),3.78(3H,s), 3.90-4.06(2H,m),4.31(1H,dd,J=13.8,4.8),4.45(1H,dd,J=13.8,6.7),4.72-4.79(1H,m),6.13(1H,brs),7.29-7.55(4H,m), 7.72-7.77(1H,m),8.80(1H,brs)
$[\alpha]^{20}_D$:-120.5° (c=0.10, MeOH)

Example 20

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(cyclohexylcarbonyl)piperidyl)carbonylamino) propanoic acid (20)

[0102]



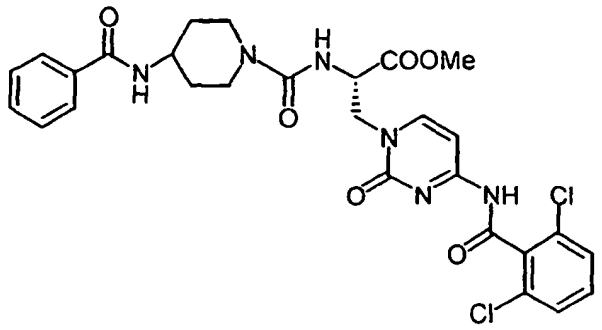
(20)

[0103] In 1.5 ml of methanol and 1.5 ml of tetrahydrofuran, 66.5 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(cyclohexylcarbonyl)piperidyl)carbonylamino) propionate was dissolved, and 1.5 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture overnight at room temperature. To the reaction solution, 2 ml of 1N hydrochloric acid and 6 ml of water were added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/ether to obtain 58.8 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(cyclohexylcarbonyl)piperidyl)carbonylamino)propanoic acid (yield: 90%). LR-MS(m/z):591(M^+-H)
IR(KBr):3418,2935,2857,1722,1631,1491,1433,1366,1304,1245,790cm^{-1}
NMR(300MHz,CD_3OD, δ ppm):1.48-1.74(10H,m),2.83-2.97(3H,m),3.50-3.59(4H,m),3.92-4.05(2H,m),4.10(1H,dd, J=13.2,9.0),4.64(1H,dd,J=13.2,4.4), 4.71(1H,dd,J=9.0,4.4),7.41-7.56(4H,m),7.95-7.78(1H,m)
HR-MS:$C_{26}H_{29}Cl_2N_6O_6$ Calcd.: Found:591.1525
$[\alpha]^{20}_D$:-138.0° (c=0.10, MeOH)

Example 21

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(phenylcarbonylamino)piperidyl) carbonylamino) propionate (21)

[0104]



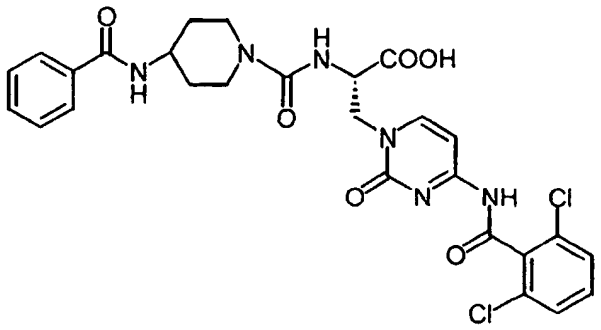
(21)

[0105] Under argon atmosphere, to a solution of 53.5 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate in 2 ml of acetonitrile and 3 ml of dichloromethane, 18 mg of saturated sodium hydrogen carbonate and 30 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, and the resulting mixture was stirred at room temperature for 4.5 hours. To the reaction mixture, 2 ml of a solution of 35 mg of phenyl-N-(4-piperidyl)carboxamide and 0.35 ml of triethylamine in acetonitrile were added, and the resulting mixture was stirred overnight at room temperature. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (dichloromethane:methanol = 30:1) to obtain 68 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(phenylcarbonylamino)piperidyl)carbonylamino) propionate (yield: 79%).
LR-MS(m/z):614(M^+)
IR(KBr):3369,2952,1739,1635,1562,1531,1492,1432,1367,1330,1302,1243,1196,11 67,1133,1075,972,790cm^{-1}
NMR(300MHz,$CDCl_3$, δ ppm):1.32-1.56(2H,m),1.93-2.05(2H,m),2.85-3.02(2H,m),3.80(3H,s),3.93-4.04(2H,m), 4.05-4.22(1H,m),4.28-4.51(2H,m),4.64-4.73(1H,m),6.49(1H,brs),7.27-7.48(4H,m),7.54-7.61(1H,m),7.76-7.85(2H,m)
$[\alpha]_D^{20}$: -137.1° (C=0.07, MeOH)

Example 22

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(phenylcarbonylamino)piperidyl) carbonylamino)propanoic acid (22)

[0106]



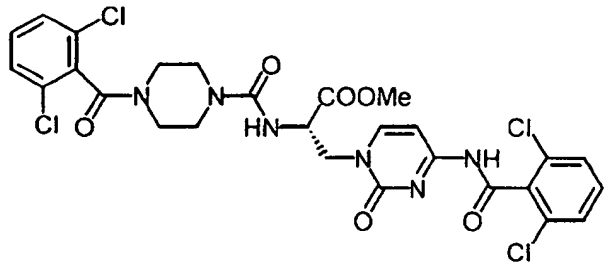
(22)

[0107] In 2 ml of methanol, 62 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(phenylcarbonylamino)piperidyl)carbonylamino) propionate was dissolved, and 0.5 ml of 1N aqueous sodium hydroxide solution was added, and the mixture was stirred at room temperature for 2 hours. To the reaction solution, 1N hydrochloric acid and water were added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/ether to obtain 53.3 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(phenylcarbonylamino)piperidyl)carbonylamino)propanoic acid (yield: 89%). LR-MS(m/z):599(M^+-H)
IR(KBr):3374,2948,1717,1636,1563,1532,1492,1431,1367,1331,1304,1244,1196, 1167,1134,1075,972,901,791cm^{-1}
NMR(300MHz,CD_3OD, δ ppm):1.30-1.54(2H,m),1.91-2.05(2H,m),2.80-3.02(2H,m),3.86-4.08(2H,m),4.10-4.22(1 H, m),4.28-4.52(2H,m),4.64-4.76(1 H,m),7.27-7.48(6H,m),7.54-7.61(1H,m),7.76-7.90(2H,m)
HR-MS:$C_{27}H_{25}Cl_2N_6O_6$ Calcd.: 599.1213, Found: 599.1214
$[\alpha]_D^{20}$: -108.0° (C=0.04, MeOH)

Example 23

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((2,6-dichlorophenyl)carbonyl) piperazinyl)carbonylamino) propionate (23)

[0108]



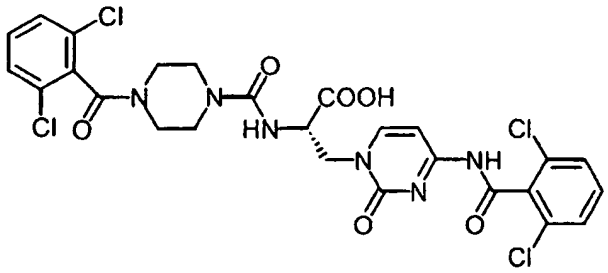
(23)

[0109] Under argon atmosphere, 48 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 2 ml of acetonitrile and 3 ml of dichloromethane, and 16 mg of saturated sodium hydrogen carbonate and 26 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 4 hours. To the reaction mixture, 30 mg of 2,6-dichlorophenylcarbonylpiperazine and 42 μl of triethylamine were added, and the resulting mixture was stirred at room temperature for 38 hours. After concentrating the reaction mixture, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 30:1) to obtain 40.9 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((2,6-dichlorophenyl)carbonyl)piperazinyl)carbonylamino) propionate (yield: 51%). LR-MS(m/z):668(M^+)
IR(KBr):3404,3081,2953,1716,1649,1562,1492,1431,1367,1303,1256,1132,1005, 795cm^{-1}
NMR(300MHz,$CDCl_3$, δ ppm):3.18-3.23(2H,m),341-3.53(4H,m),3.78(3H,s),3.76-3.82(2H,m),4.21-4.44(2H,m), 4.71-4.80(1H,m),6.70-6.79(1H,m),7.22-7.41(6H,m),7.57(1H,brs),7.80-7.84(1H,m),9.16(1H,brs)
$[\alpha]_D^{20}$: -118.6° (C=0.11, MeOH)

Example 24

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((2,6-dichlorophenyl)carbonyl)piperazinyl) carbonylamino) propanoic acid (24)

[0110]



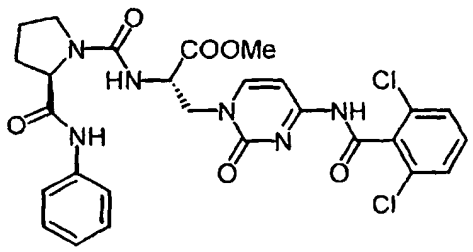
(24)

[0111] In 2 ml of methanol, 35 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-benzylpiperidyl)carbonylamino) propionate was dissolved, and 0.25 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 2 hours. To the reaction solution, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/n-hexane to obtain 26 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-((2,6-dichlorophenyl)carbonyl)piperazinyl)carbonylamino) propanoic acid (yield: 79%).
LR-MS(m/z):653(M^+-H)
IR(KBr):3389,3081,2925,1718,1636,1564,1492,1430,1366,1257,1196,1132,1003,90 1,795cm^{-1}
NMR(300MHz,CD_3OD, δ ppm):3.22-3.28(2H,m),3.42-3.58(4H,m),3.80-3.87(2H,m),4.25-4.37(1H,m),4.42-4.51(1H, m),4.60-4.64(1H,m),7.28-7.40(8H,m),7.60(1H,brs),7.82(1H,brs)
HR-MS:$C_{26}H_{21}C_{14}N_6O_6$ Calcd.: 653.0277, Found: 653.0273
$[\alpha]_D^{20}$: -99.0° (C=0.05, MeOH)

Example 25

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylcarbonyl)pyrrolidinyl) carbonylamino) propionate (25)

[0112]



(25)

[0113] Under argon atmosphere, 59 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 2 ml of acetonitrile and 3 ml of dichloromethane, and 21 mg of saturated sodium hydrogen carbonate and 34 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 4 hours. To the reaction mixture, 34 mg of N-phenylpyrrolidin-2-ylcarboxamide and 53 μl of triethylamine were added, and the resulting mixture was stirred at room temperature for 12 hours. After concentrating the reaction mixture, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue

was purified by column chromatography (dichloromethane/methanol = 20:1) to obtain 63.8 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylcarbonyl)pyrrolidinyl)carbonylamino) propionate (yield: 62%).

LR-MS(m/z):600(M^+)

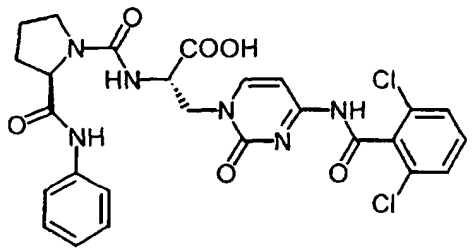
IR(KBr):3395,2958,1652,1559,1495,1433,1367,1307,1248,1194,902,792,759cm^{-1} NMR(300MHz,$CDCl_3$, δ ppm): 1.78-2.18(3H,m),2.42-2.53(1H,m),3.23-3.36(1 H,m),3.41-3.50(1H,m),3.78(3H,s),4.25-4.43(2H,m),4.57-4.76(2H,m), 6.42-6.50(1H,m),7.01-7.06(1H,m),7.22-7.40(5H,m),7.41-7.58(2H,m),7.78-7.81(1H,m),8.99(1H,brs),9.42(1H,brs)

$[\alpha]_D^{20}$: -91.4° (C=0.08, MeOH)

Example 26

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylcarbonyl)pyrrolidinyl)carbonylamino) propanoic acid (26)

[0114]



(26)

[0115] In 2 ml of methanol, 59 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylcarbonyl)pyrrolidinyl)carbonylamino) propionate was dissolved, and 0.5 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 3.5 hours. To the reaction solution, 1N hydrochloric acid was added and the mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/n-hexane to obtain 49.6 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2-(phenylcarbonyl)pyrrolidinyl)carbonylamino)propanoic acid (yield: 84%). LR-MS(m/z):585(M^+-H)

IR(KBr):3395,2958,1652,1559,1495,1433,1367,1307,1248,1194,902,792,759cm^{-1}

NMR(300MHz,CD_3OD, δ ppm):1.60-2.42(4H,m),3.21-3.35(1H,m),3.40-3.58(1H,m),4.21-4.38(1H,m),4.40-4.55(2H, m),4.62-4.74(1H,m),7.01-7.10(1H,m),7.22-7.65(8H,m),7.87(1H,brs),9.20(1H,brs)

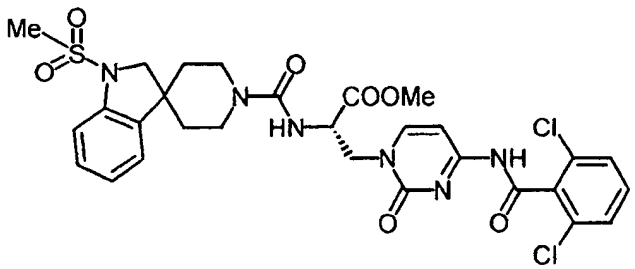
HR-MS:$C_{26}H_{23}Cl_2N_6O_6$ Calcd.: 585.1056, Found: 585.1034

$[\alpha]_D^{20}$: -68.2° (C=0.04, MeOH)

Example 27

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydrpyrimidinyl)-2-((1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino) propionate (27)

[0116]

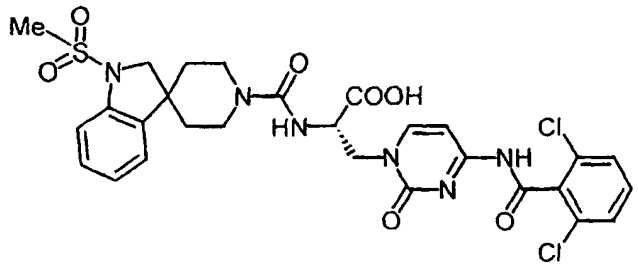


(27)

[0117] Under argon atmosphere, 60 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 2 ml of acetonitrile and 4 ml of dichloromethane, and 22 mg of saturated sodium hydrogen carbonate and 36 mg of chloroformic acid p-nitrophenyl ester were added to the mixture while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 4 hours. To the reaction mixture, 51 mg of 1-(methylsulfonyl)spiro[indoline-3,4'-piperidine] and 56 µl of triethylamine were added, and the resulting mixture was stirred at room temperature for 12 hours. After concentrating the reaction mixture, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 30:1) to obtain 65 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydrpyrimidinyl)-2-((1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino) propionate (yield: 60%).
LR-MS(m/z):676(M^+)
IR(KBr):3410,2930,1738,1716,1657,1562,1492,1433,1345,1304,1247,1159,1049,
984, 775cm^{-1}
NMR(300MHz,$CDCl_3$,ppm):1.64-1.87(4H,m),2.82-2.95(2H,m),2.92(3H,s), 3.78(3H,s),3.84(2H,s),3.90-4.02(2H,m), 4.28-4.46(2H,m),4.75-4.82(1H,m),6.47-6.56(1H,m),7.02-7.43(7H,m),7.57(1H,brs),7.83-7.92(1H,m),9.15(1H,brs)
$[\alpha]_D^{20}$: -120.7° (C=0.14, MeOH)

Example 28

[0118] 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino)propanoic acid (28)



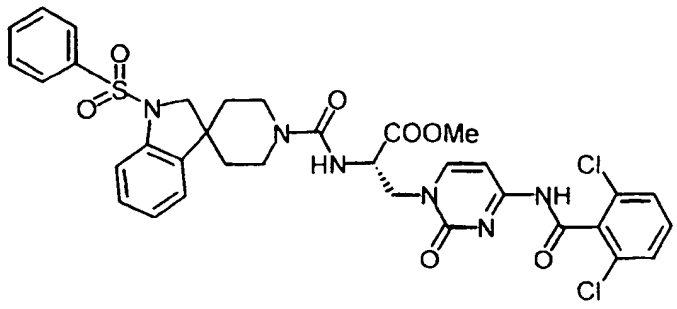
(28)

[0119] In 3 ml of methanol, 58 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino) propionate was dissolved, and 0.5 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 3.5 hours. To the reaction mixture, 1N hydrochloric acid was added, and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/n-hexane to obtain 48.4 mg of 3-(4-((2,6-dichlorophenyl) carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino)propanoic acid (yield: 85%).
LR-MS(m/z):661(M^+-H) IR(KBr):3413,2931,1716,1629,1564,1493,1431,1343,1248,1158,1050,961,901,777c m^{-1}
NMR(300MHz,CD_3OD, δ ppm):1.63-1.98(4H,m),2.93-3.10(2H,m),2.95(3H,s),3.84(2H,s),3.94-4.18(2H,m),4.32-4.68 (3H,m),7.01-7.50(9H,m),7.65(1H,brs),8.16(1H,brs)
HR-MS:$C_{28}H_{27}Cl_2N_6O_7S$ Calcd.:661.1039, Found: 661.1069
$[\alpha]_D^{20}$: -136.4° (C=0.04, MeOH)

Example 29

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino) propionate (29)

[0120]



(29)

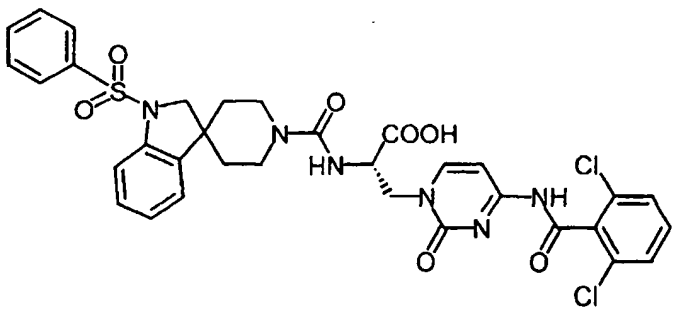
[0121] Under argon atmosphere, 51.5 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 2 ml of acetonitrile and 3 ml of dichloromethane, and 18 mg of saturated sodium hydrogen carbonate and 28 mg of chloroformic acid p-nitrophenyl ester were added to the mixture, followed by stirring the resulting mixture at room temperature for 6.5 hours. To the reaction mixture, 53 mg of 1-(phenylsulfonyl) spiro[indoline-3,4'-piperidine] and 46 μl of triethylamine were added, and the resulting mixture was stirred at room temperature for 12 hours. After concentrating the reaction mixture, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 50:1) to obtain 83.9 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino) propionate (yield: 87%).
LR-MS(m/z):738(M^+)
IR(KBr):3291,3069,2949,1715,1657,1561,1491,1433,1363,1308,1244,1169,1048, 986,926,790,757,739cm^{-1}
NMR(300MHz,$CDCl_3$, δ ppm):1.15-1.24(2H,m),1.52-1.67(2H,m),2.71-2.84(2H,m),3.74(3H,s),3.79(2H,m),3.76-3.88(2H,m),4.26-4.42(2H,m),4.71-4.80(1H,m),6.38-6.41(1H,m),6.98-7.06(2H,m),7.20-7.60(8H,m),7.65(1H,brs),7.77-7.83(1 H.m),9.04(1H,brs)
$[\alpha]_D^{20}$: -130.0° (C=0.11, MeOH)

Example 30

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino)propanoic acid

[0122]

(30)



(30)

[0123] In 1 ml of methanol, 76 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(methylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino) propionate was dissolved, and 0.5 ml of 1N sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 30 hours. To the reaction solution, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/ether to obtain 62.5 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((1-(phenylsulfonyl)spiro[indoline-3,4'-piperidin]-10-yl)carbonylamino)propanoic acid (yield: 86%).

LR-MS(m/z):723(M^+-H)

IR(KBr):3409,2937,1717,1629,1563,1492,1432,1361,1307,1253,1167,1092,984,927, 791,758cm^{-1}

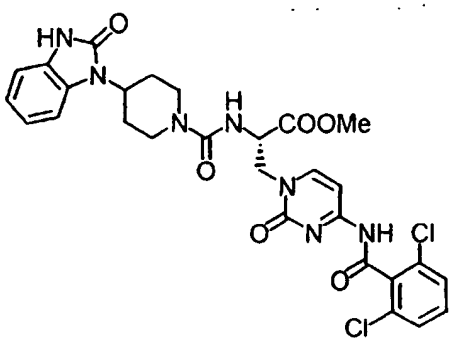
NMR(300MHz,CD_3OD, δ ppm):1.17-1.31(2H,m),1.52-1.70(2H,m),2.71-2.90(2H,m),3.70-3.90(4H,m),4.24-4.52(2H, m),4.63-4.82(1H,m),6.65-7.08(2H,m),7.20-7.70(11H,m),7.75-7.88(2H,m),7.99(1H,brs)

$[\alpha]_D^{20}$: -54.2° (C=0.05, MeOH)

Example 31

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl) carbonylamino) propionate (31)

[0124]



(31)

[0125] Under argon atmosphere, 156 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 10 ml of acetonitrile and 10 ml of dichloromethane, and 52.4 mg of sodium hydrogen carbonate and 92.2 mg of chloroformic p-nitrophenyl ester were added thereto while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 3 hours. To the reaction mixture, 12 ml of a solution of 176 mg of 4-(2-keto-1-benzimidazolinyl)piperidine and 0.35 ml of triethylamine in dichloromethane were added, and the resulting mixture was stirred overnight at room temperature. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (chloroform/methanol to obtain 128 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino) propionate (yield: 50%).

LR-MS(m/z):627(M^+)

IR(KBr):3057,2953,2847,1686,1628,1487,1433,1369,1308,1266,1246,1196,1133, 1013,897,797,736cm^{-1}

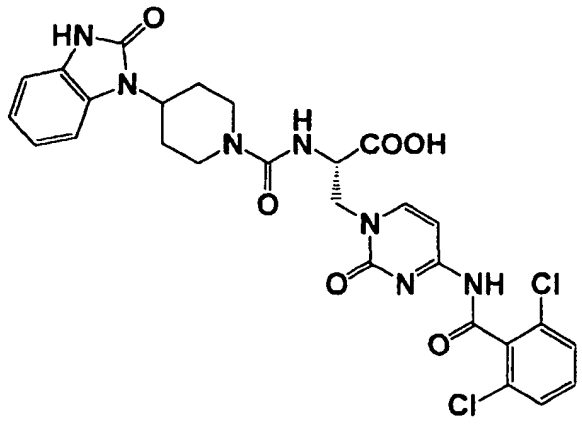
NMR(300MHz,CD_3OD, δ ppm):1.74-1.84(2H,m),2.31-2.48(2H,m),2.93-3.08(2H,m),3.81(3H,s),4.11-4.23(3H,m), 4.42-4.57(1H,m),4.61-4.74(2H,m),7.03-7.12(3H,m),7.25-7.30(1H,m),7.40-7.51(3H.m),7.55-7.62(1H,m),8.03-8.05 (1H,m)

$[\alpha]^{20}_D$:-144.6° (c=0.03,MeOH)

Example 32

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl) carbonylamino)propanoic acid (32)

[0126]



(32)

[0127] In 3.0 ml of methanol, 112.6 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino) propionate was dissolved, and 1 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 5 hours. To the reaction solution, 1.2 ml of 1N hydrochloric acid and 8 ml of water were added, and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from methanol/ether to obtain 103.4 mg of 3-(4-((2,6-dichlorophenyl) carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid (yield: 94%).

LR-MS(m/z):612(M^+-H)

IR(KBr):3398,2931,2862,1691,1659,1487,1430,1367,1303,1245,1193,1011,899,792, 756cm^{-1}

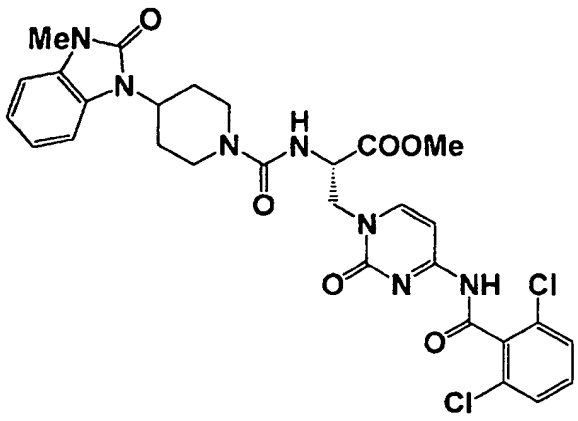
NMR(300MHz,CD_3OD, δ ppm):1.72-1.84(2H,m),2.30-2.48(2H,m),2.93-3.07(2H,m),4.11-4.22(3H,m),4.42-4.57(1H, m),4.65-4.76(2H,m),7.00-7.12(3H,m),7.24-7.30(1H,m),7.40-7.51(3H,m),7.55-7.62(1H,m),8.03-8.05(1H,m) HR-MS: $C_{27}H_{24}Cl_2N_7O_6$ Calcd.: 612.1165, Found: 612.1146

$[\alpha]^{20}_D$:-135.1° (c=0.07,MeOH)

Example 33

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methyl-2-oxo-3-azaindolinyl) piperidyl)carbonylamino) propionate (33)

[0128]



(33)

[0129] Under argon atmosphere, 55 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 2 ml of acetonitrile and 3 ml of dichloromethane, and 18.5 mg of saturated sodium hydrogen carbonate and 30.2 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 4 hours. To the reaction mixture, 39.3 mg of 1-methyl-3-(4-piperidyl)-3-hydrobenzimidazol-2-one and 49 μl of triethylamine were added, and the resulting mixture was stirred at room temperature for 14 hours. After concentrating the reaction mixture, saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (dichloromethane/methanol = 30:1) to obtain 65 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3 -methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino) propionate (yield: 68%).

LR-MS(m/z):641(M^+)

IR(KBr):3423,3071,2952,1660,1562,1495,1434,1368,1305,1247,1197,1132,1053, 986,903,791,753,743,700cm^{-1}

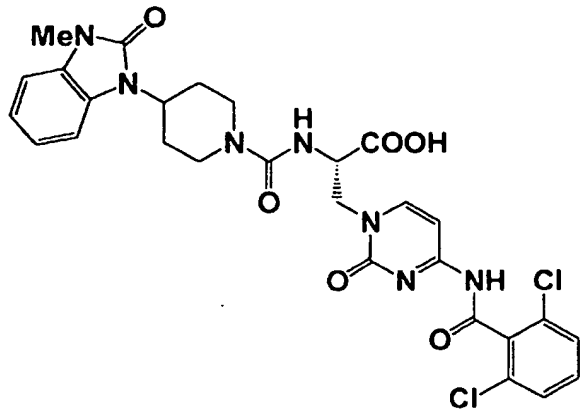
NMR(300MHz,$CDCl_3$, δ ppm): 1.72-1.84(2H,m),2.26-2.48(2H,m),2.80-2.97(2H,m),3.31(3H,s),3.76(3H,m),4.06-4.20 (2H,m),4.31-4.49(3H,m),4.80-4.88(1H,m),6.40-6.55(1H,m),6.93-7.20(5H,m),7.22-7.40(4H,m),7.58(1H,brs),7.81-7.88 (1H.m),9.56(1H,brs)

$[\alpha]_D^{20}$: -139.4° (C=0.11, MeOH)

Example 34

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl) carbonylamino)propanoic acid (34)

[0130]



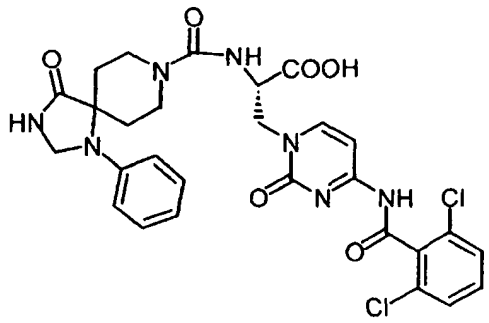
(34)

[0131] In 2 ml of methanol, 59 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino) propionate was dissolved, and 0.5 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for 4 hours. To the reaction mixture, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/ether to obtain 47.3 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(3-methyl-2-oxo-3-azaindolinyl)piperidyl)carbonylamino)propanoic acid (yield: 84%).
LR-MS(m/z):627(M^+)
IR(KBr):3406,2937,1655,1563,1494,1434,1397,1367,1306,1247,1196,1163,1 132,10 52,986,900,791,753cm^{-1}
NMR(300MHz,CD_3OD, δ ppm):1.75-1.96(2H,m),2.22-2.48(2H,m),2.83-3.05(2H,m),3.40(3H,s),4.03-4.22(2H,m), 4.32-4.58(3H,m),4.70-4.84(1H,m),6.94-7.40(9H,m),7.65(1H,brs),8.04(1H,brs)
HR-MS:$C_{28}H_{28}Cl_2N_7O_6$ Calcd.: 628.1478, Found: 628.1437
$[\alpha]_D^{20}$: -118.3° (C=0.05, MeOH)

Example 35

2-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dichlorophenylcarbonylamino)-2-oxohydropyrimidinyl)propanoic acid (35)

[0132]



(35)

[0133] Under argon atmosphere, methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate (40mg, 0.104mmol) was dissolved in 0.5 ml of THF, and 2,4,8-triaza-1-oxo-4-phenylspiro[4.5]decane-8-car-

bonyl chloride (61.0mg, 0.208mmol) and triethylamine (29 μl, 0.208mmol) were added thereto, followed by stirring the resulting mixture at room temperature for 12 hours. To the reaction mixture, IN hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in 4 ml of methanol, and 0.5 ml of 1N aqueous sodium hydroxide solution was added thereto, followed by stirring the resulting mixture at room temperature for 12 hours. To the reaction mixture, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by column chromatography (ethyl acetate/methanol = 15/1) to obtain 2-((2,4,8-triaza-1-oxo-4-phenylspiro[4.5]dec-8-yl)carbonylamino)-3-(4-((2,6-dichlorophenylcarbonylamino)-2-oxohydropyrimidinyl)propanoic acid (30.4 mg) (yield: 54%).

LR-MS(m/z):628(M^++H)

IR(KBr):3423, 2923, 1709,1627, 1494, 1432, 1367, 1305, 1252cm^{-1} NMR(300MHz,CD3OD δ ppm):1.63-1.72 (m, 2H), 2.45-2.64 (m, 2H), 3.50-3.70 (m, 2H), 3.87-3.95 (m, 2H), 4.10-4.20 (m, 1H), 4.60-4.80 (m, 2H), 4.70 (s, 2H), 6.75-6.82 (m, 3H), 7.23 (d, J=8.1 Hz, 1H), 7.26 (d, J=7.2 Hz, 1H), 7.42-7.55 (m, 4H), 7.99 (d, J=7.2 Hz, 1H).

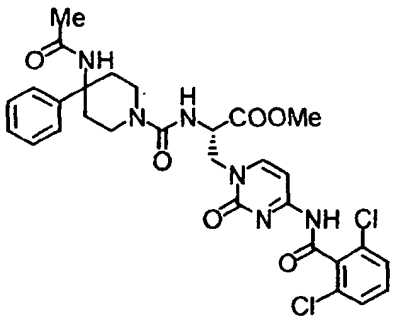
HR-MS:$C_{28}H_{27}Cl_2N_7O_6$ Calcd.: 628.1478, Found: 628.1440

$[\alpha]^{20}_D$:-87.7° (c=0.42,MeOH)

Example 36

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl) carbonylamino) propionate (36)

[0134]



(36)

[0135] Under argon atmosphere, to a solution of 87.2 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate trifluoroacetic acid salt in 5 ml of acetonitrile and 5 ml of dichloromethane, 36.7 mg of sodium hydrogen carbonate and 47.6 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, and the resulting mixture was stirred at room temperature for 3 hours. To the reaction mixture, 3.5 ml of a solution of 59.2 mg of 4-acetoamide-4-phenylpiperidine and 0.15 ml of triethylamine in dichloromethane was added, and the resulting mixture was stirred overnight at room temperature. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (chloroform/methanol = 20:1) to obtain 36.6 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl)carbonylamino) propionate (yield: 33%).

LR-MS(m/z):628(M^+)

IR(KBr):3353,3075,2982,2856,1732,1658,1560,1493,1432,1367,1301,1259,1131, 985,789cm^{-1}

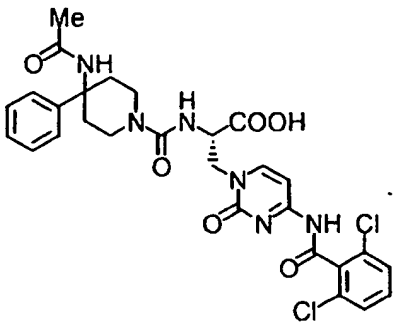
NMR(300MHz,CD_3OD, δ ppm):1.85-1.96(2H,m),2.01(3H,s),2.36-2.46(2H,m),3.10-3.21(2H,m),3.77(3H,s),3.80-3.90 (2H,m),4.13(1H,dd,J=13.2,9.1), 4.62(1H,dd,J=13.2,4.7),4.72(1H,dd,J=9.1,4.7),7.15-7.23(1H,m),7.28-7.58(8H,m). 7.94-7.99(1H.m),8.19(1H,brs)

$[\alpha]^{20}_D$:-111.2° (c=0.03,MeOH)

Example 37

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl) carbonylamino)propanoic acid (37)

[0136]



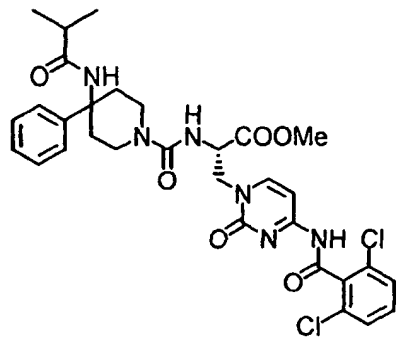
(37)

[0137] In 1.5 ml of methanol, 33.7 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl)carbonylamino) propionate was dissolved, and 0.35 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the mixture at room temperature for 5.5 hours. To the reaction solution, 4 ml of 0.1N hydrochloric acid was added, and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from methanol/ether to obtain 30.2 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid (yield: 91%).
LR-MS(m/z):613(M^+-H)
IR(KBr):3372,3075,2935,1722,1657,1560,1493,1431,1367,1303,1261,1195,1132, 986,901,790cm^{-1}
NMR(300MHz,CD_3OD, δ ppm):1.86-1.99(2H,m),2.01(3H,s),2.36-2.45(2H,m),3.09-3.23(2H,m),3.82-3.93(2H,m),4.12 (1H,dd,J=13.2,9.5),4.66(1H,dd,J=13.2,4.2), 4.74(1H,dd,J=9.5,4.2),7.15-7.22(1H,m),7.27-7.58(8H,m),7.93-7.98(1H, m), 8.19(1H,brs)

Example 38

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-methylpropanoylamino)-4-phenylpiperidyl)carbonylamino)propanoic acid (38)

[0138]



(38)

[0139] Under argon atmosphere, to a solution of 58.9 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrmidinyl) propionate in 4 ml of acetonitrile, 19.3 mg of sodium hydrogen carbonate and 37.0 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, and the resulting mixture was stirred at room temperature for 2.5 hours. To the reaction mixture, 3 ml of a solution of 52.8 mg of 2-methyl-N-(4-phenyl (4-piperidyl))propanamide and 0.11 ml of triethylamine in acetonitrile was added, and the resulting mixture was stirred

at room temperature for 7 hours. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (chloroform:methanol = 30:1) to obtain 83.2 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-methylpropanoylamino)-4-phenylpiperidyl) carbonylamino)propanoic acid (yield: 82%).

LR-MS(m/z):656(M^+)

IR(KBr):3319,3013,2968,1741,1657,1564,1532,1494,1433,1368,1306,1242,1210, 1132,991,928,902,755cm^{-1}

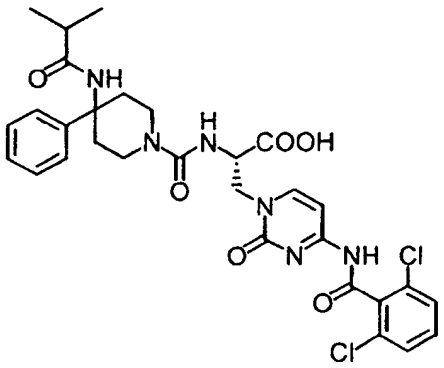
NMR(300MHz,$CDCl_3$, δ ppm):1.07(6H,d,J=6.9),1.86-2.00(2H,m),230-2.46(3H,m),3.03-3.18(2H,m),3.74(3H,s), 3.72-3.84(2H,m),4.25-4.44(2H,m),4.72-4.79(1H,m),5.83-5,90(1H,m),6.58(1H,brs),7.16-7.35(8H,m),7.52(1H,brs), 7.77-7.81(1H,m),9.22(1H,brs)

$[\alpha]^{20}_D$:-144.3° (c=0.20,MeOH)

Example 39

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-methylpropanoylamino)-4-phenylpiperidyl) carbonylamino)propanoic acid (39)

[0140]



(39)

[0141] In 2 ml of methanol, 78.5 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-methylpropanoylamino)-4-phenylpiperidyl)carbonylamino) propionate was dissolved, and 1 ml of aqueous sodium hydroxide solution was added thereto, followed by stirring the resulting mixture overnight at room temperature. To the reaction solution, 1 ml of 1N hydrochloric acid and 4 ml of water were added, and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from methanol/ether to obtain 71.6 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(2-mcthylpropanoylamino)-4-phenylpiperidyl) carbonylamino)propanoic acid (yield: 93%).

LR-MS(m/z):641(M^+-H)

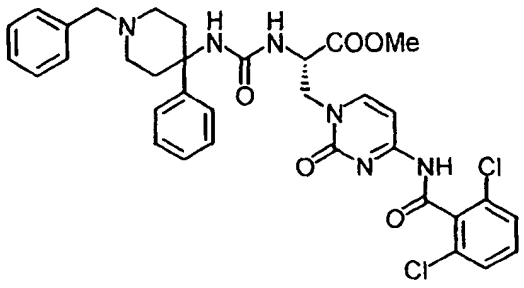
IR(KBr): 3380,2968,2935,2869,1721,1657,1493,1429,1366,1303,1248,1193, 1131,989, 901 cm^{-1}

NMR(300MHz,CD_3OD, δ ppm):1.09(6H,d,J=6.9),1.83-1.99(2H,m),237-2.51(2H,m),2.59-2.68(1H,m),,3.05-3.20(23H, m),3.82-3.94(2H,m),4.06-4.17(1 H,m),4.62-4.78(2H,m),7.17-7.22(1H,m),7.28-7.59(7H,m),7.97-8.05(2H,m)

Example 40

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-phenyl-1-benzyl-4-piperidyl) carbonylamino) propionate (40)

[0142]



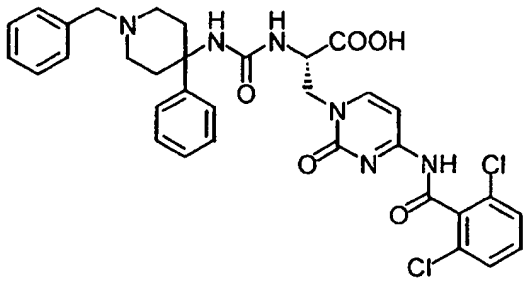
(40)

[0143] Under argon atmosphere, to a solution of 58.7 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate in 4 ml of acetonitrile and 4 ml of dichloromethane, 19.2 mg of saturated sodium hydrogen carbonate and 38.3 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, and the resulting mixture was stirred at room temperature for 2.5 hours. To the reaction mixture, 6 ml of a solution of 90.7 mg of 1-benzyl-4-amino-4-phenylpiperidine and 0.11 ml of triethylamine in acetonitrile was added, and the resulting mixture was stirred overnight at room temperature. After concentrating the reaction mixture, 10 ml of saturated aqueous sodium hydrogen carbonate solution was added and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline. dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (chloroform/methanol) to obtain 90.7 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-phenyl-1-benzyl-4-piperidyl)carbonylamino) propionate (yield: 88%).
LR-MS(m/z):676(M^+)
IR(KBr):3305,3061,3027,2947,2811,2773,1717,1654,1558,1489,1431,1367,1299, 1244,1131,996,900,795,751cm^{-1}
NMR(300MHz,$CDCl_3$, δ ppm):2.04-2.43(6H,m),2.73-2.81(2H,m),3.55(2H,s), 3.74(3H,s),4.21(1H,dd,J=13.3,5.9),4.35 (1H,dd,J=13.3,5.9),4.44-4.52(1H,m), 6.02(H,brs),7.20-7.54(16H,m)

Example 41

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-phenyl-1-benzyl-4-piperidyl)carbonylamino) propanoic acid (41)

[0144]



(41)

[0145] In 1.5 ml of methanol, 66.1 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-(methylamino)-4-phenylpiperidyl)carbonylamino) propionate was dissolved, and 1.5 ml of 1N aqueous sodium hydroxide solution was added thereto, followed by stirring the resulting mixture overnight at room temperature. To the reaction solution, 1.5 ml of 1N hydrochloric acid and 10 ml of water were added, and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate

and concentrated. The residue was reprecipitated from chloroform/ether to obtain 28.7 mg of 3-(4-((2,6-dichlorophenyl) carbonylamino)-2-oxohydropyrimidinyl)-2-(((4-phenyl-1-benzyl-4-piperidyl)carbonylamino)propanoic acid (yield: 44%).

LR-MS(m/z):661(M^+-H)

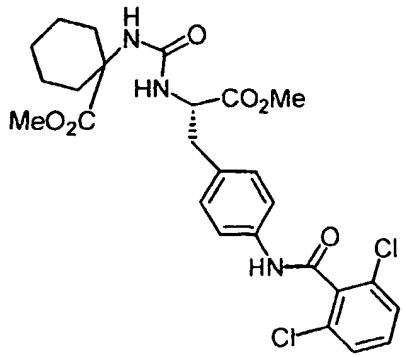
IR(KBr):3391,2944,2810,1657,1623,1564,1495,1430,1364,1302,1246,1133,794cm^{-1}

NMR(300MHz,CD_3OD, δ ppm):1.98-2.17(2H,m),2.23-2.44(2H,m),2.70-3.12(4H,m),3.78-4.00(3H,m),4.45-4.65(2H, m),7.10-7.18(1H,m),7.22-7.53(13H,m),7.90-7.98(1H,m)

Example 42

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl-2-((((methoxycarbonyl)cyclohexyl)amino)carbonylamino) propionate (42)

[0146]



(42)

[0147] Under argon atmosphere, to a solution of 208 mg of di-t-butyl dicarbonate and 137 mg of 4-(N,N-dimethyl-amino)pyridine in 1 ml of acetonitrile, a solution of 170 mg of methyl 1-aminocyclohexane carboxylate in 2 ml of acetonitrile was added, and the resulting mixture was stirred at room temperature for 40 minutes. To the reaction mixture, a solution of 261 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate in 10 ml of acetonitrile was added, and the resulting mixture was stirred at room temperature for 19 hours. To the reaction mixture, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/n-hexane = 2:1) to obtain 317 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl-2-((((methoxycarbonyl)cyclohexyl)amino)carbonylamino) propionate (yield: 86%). m.p.: 255°C

LR-MS(m/z):550(M^+)

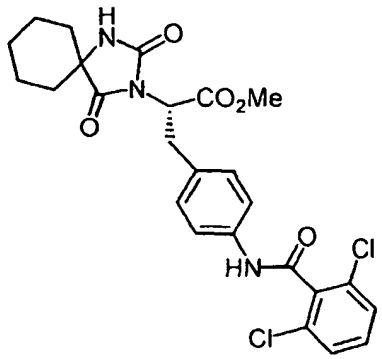
IR(KBr):3435,3307,3125,2938,2858,1772,1747,1712,1664,1604,1538,1520,1432, 1322,1270,1255,1196,799,779cm^{-1}

NMR(300MHz,DMSO-d_6, δ ppm):1.09-1.65(8H,m), 1.82(2H,m), 2.87(1H,dd,J=6.9, 13.7Hz), 2.96(1H,dd,J=5.5, 13.7Hz), 3.51(3H,s), 3.63(3H,s), 4.39(1H,m), 6.16(1H,d,J=8.5Hz), 6.49(1H,s), 7.11(1H,d,J=8.5Hz), 7.45-7.62(5H,m), 10.69(1H,s)

Example 43

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl-2-((((methoxycarbonyl)cyclohexyl)amino)carbonylamino) propionate (43)

[0148]



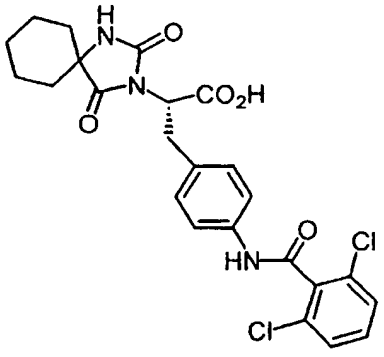
(43)

[0149] Under argon atmosphere, 278 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl-2-((((methoxycarbonyl)cyclohexyl)amino)carbonylamino) propionate was dissolved in 10 ml of methanol and 10 ml of tetrahydrofuran, and 2 mg of potassium t-butoxide was added thereto, followed by stirring the resulting mixture at room temperature for 16 hours. After concentrating the reaction mixture, 1N hydrochloric acid was added to the residue and the resulting mixture was extracted with chloroform. Organic phases were combined, washed with water and with saturated saline, dried over anhydrous magnesium sulfate and concentrated. The residue was crystallized from ethyl acetate to obtain 177 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl-2-((((methoxycarbonyl)cyclohexyl)amino) carbonylamino) propionate (yield: 68%). m.p.: 191°C
LR-MS(m/z):518(M^+)
IR(KBr): 3414,3333,3273,324,3186,3121,3073,2947,2938,2857,1738,1676, 1653, 1608,1550,1510,1433,1414,1367,1332,1279,1238,1219,1195,1170,1140,1062, 785 cm^{-1}
NMR(300MHz,DMSO-d_6, δ ppm):1.05-1.70(10H,m), 3.15-3.35(2H,m), 3.68(3H,s), 4.88(1H,dd,J=5.1, 11.7Hz), 7.10 (2H,d,J=8.5Hz), 7.45-7.58(5H,m), 8.68(1H,bs), 10.65(1H,s)

Example 44

3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl-2-((((methoxycarbonyl)cyclohexyl)amino)carbonylamino)propanoic acid (44)

[0150]



(44)

[0151] In 5 ml of methanol and 5 ml of tetrahydrofuran, 70 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino) phenyl-2-((((methoxycarbonyl)cyclohexyl)amino)carbonylamino) propionate was dissolved, and 0.5 ml of 1N aqueous sodium hydroxide solution was added, followed by stirring the resulting mixture at room temperature for I hour. After

concentrating the reaction mixture, 1N hydrochloric acid was added to the residue and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with water and with saturated saline, dried over anhydrous magnesium sulfate and concentrated. The residue was recrystallized from ethyl acetate/n-hexane to obtain 48 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)phenyl-2-((((methoxycarbonyl)cyclohexyl)amino)carbonylamino) propanoic acid (yield: 70%). m.p.: 250°C

LR-MS(m/z):504(M^+)

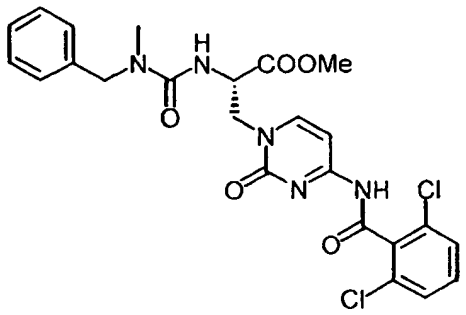
IR(KBr):3293,3125,3068,2938,2863,1761,1710,1670,1604,1537,1520,1434,1415, 1368,1322,1304,1270,1195,776cm^{-1}

NMR(300MHz,DMSO-d_6, δ ppm):1.05-1.65(10H,m), 3.18-3.32(2H,m), 4.72(1H,m), 7.10(2H,d,J=8.2Hz), 7.45-7.58(5H, m), 8.61(1H,bs), 10.64(1H,s), 13.12(1H,bs)

Example 45

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methylbenzylamino)carbonylamino) propionate (45)

[0152]



(45)

[0153] Under argon atmosphere, 38.5 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 2 ml of THF, and 59.0 mg of chloro-N-methyl-N-benzylamide and 125 ml of triethylamine were added thereto, followed by stirring the resulting mixture at room temperature for 3 days. To the reaction solution, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated aqueous sodium hydrogen carbonate solution and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/methanol = 20:1) to obtain 36.2 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methylbenzylamino)carbonylamino) propionate (yield: 68%).

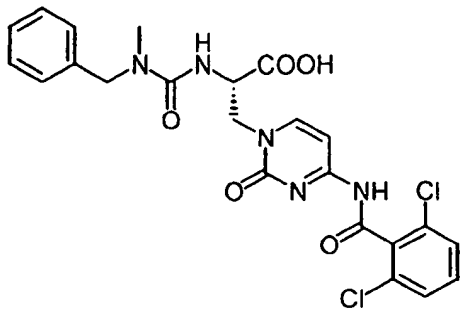
LR-MS(m/z):531(M^+)

NMR(300MHz,CD_3OD, δ ppm):2.85(3H,s),3.78(3H,s),4.06-4.19(1H,m),4.38-4.60(2H,m),4.57-4.66(1H,m),4.72-4.78 (1H,m),7.18-7.28(3H,m),7.30-7.38(2H,m),7.41-7.55(4H,m),7.88-7.92(1H,m)

Example 46

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methylbenzylamino)carbonylamino)propanoic acid (46)

[0154]



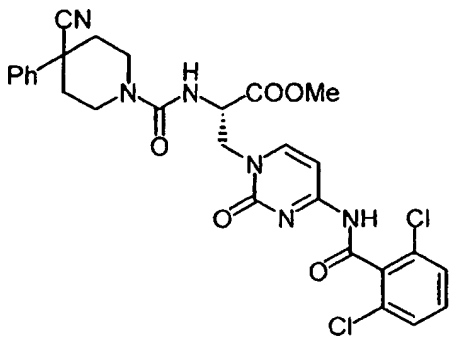
(46)

[0155] In 1 ml of methanol, 59.6 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methylbenzylamino)carbonylamino) propionate was dissolved, and 0.3 ml of 1N aqueous sodium hydroxide solution was added thereto, followed by stirring the resulting mixture overnight. To the reaction solution, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/ether to obtain 35.4 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((methylbenzylamino)carbonylamino)propanoic acid (yield: 61%).
LR-MS(m/z):517(M^+)
IR(KBr):3423,1718,1628,1561,1493,1432,1366,1305,1247,790cm^{-1}
NMR(300MHz,CD_3OD, δ ppm):2.85(3H,s),4.07-4.16(1H,m),4.37-4.60(2H,m),4.63-4.70(1H,m),4.73-4.80(1H,m), 7.15-7.25(3H,m),7.27-7.38(2H,m),7.40-7.54(4H,m), 7.90-7.94(1H,m)

Example 47

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-cyano-4-phenylpiperidyl) carbonylamino) propionate (47)

[0156]



(47)

[0157] Under argon atmosphere, 69.3 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 0.5 ml of acetonitrile and 1 ml of dichloromethane, and 27.2 mg of sodium hydrogen carbonate and 43.5 mg of chloroformic acid p-nitrophenyl ester were added thereto while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 1 hour. To the reaction mixture, 52.1 mg of 4-phenylpiperidine-4-carbonitrile and 100 ml of triethylamine were added, and the resulting mixture was stirred overnight. Aqueous potassium carbonate solution was added to the reaction solution, and the resulting mixture was ex-

tracted with ethyl acetate. Organic phases were combined, washed with 1N hydrochloric acid and with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/methanol = 20:1) to obtain 54.5 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-cyano-4-phenylpiperidyl)carbonylamino) propionate (yield: 51%).

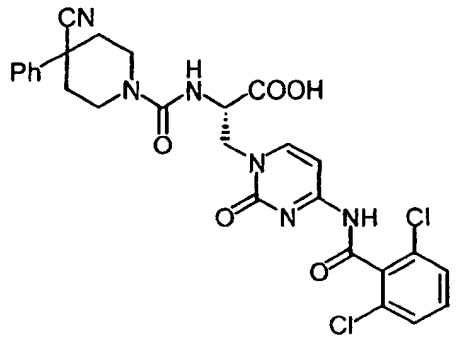
LR-MS(m/z):596(M^+-H)

NMR(300MHz,$CDCl_3$, δ ppm):1.90-2.16(4H,m),3.21-3.33(2H,m),3.79(3H,m),4.08-4.18(2H,m),4.37-4.40(2H,m), 4.73-4.81(1H,m),6.58(1H,brs),7.30-7.60(9H,m), 7.73-7.78(1H,m),8.40(1H,brs)

Example 48

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-cyano-4-phenylpiperidyl)carbonylamino) propanoic acid (48)

[0158]



(48)

[0159] Under argon atmosphere, 46.5 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-cyano-4-phenylpiperidyl)carbonylamino) propionate was dissolved in 1.0 ml of methanol, and 0.24 ml of 1N aqueous sodium hydroxide solution was added thereto, followed by stirring the resulting mixture overnight. To the reaction solution, 1N hydrochloric acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/ether to obtain 35.5 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((4-cyano-4-phenylpiperidyl)carbonylamino)propanoic acid (yield: 78%).

LR-MS(m/z):581(M^+)

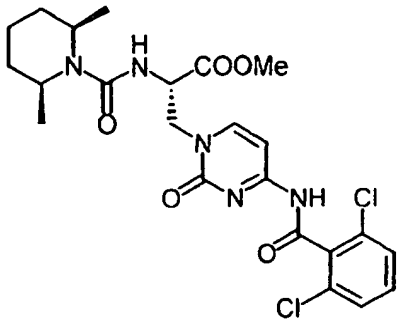
IR(KBr):3423,2927,1724,1655,1624,1558,1493,1432,1366,1242cm^{-1}

NMR(300MHz,CD_3OD, δ ppm):1.99-2.15(4H,m).3.15-3.30(2H,m),4.08-4.21 (3H,m),4.61-4.69(1H,m),4.72-4.78(1H, m),7.29-7.58(9H,m),7.98-8.02(1H,m)

Example 49

Methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethylpiperidyl)carbonylamino) propionate (49)

[0160]



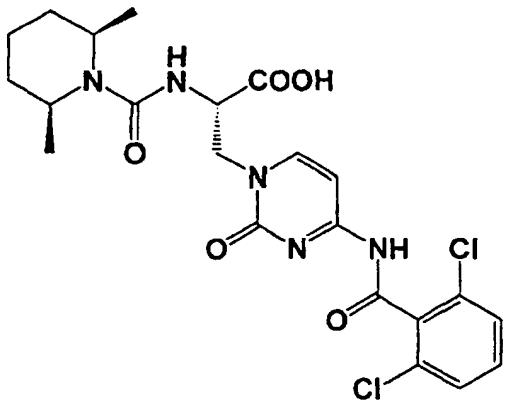
(49)

[0161] Under argon atmosphere, 75.0 mg of methyl 2-amino-3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl) propionate was dissolved in 1.0 ml of acetonitrile and 2 ml of dichloromethane, and 29.5 mg of sodium hydrogen carbonate and 47.2 mg of chloroformic acid p-nitrophenyl ester were added while cooling the mixture in ice, followed by stirring the resulting mixture at room temperature for 1 hour. To the reaction mixture, 34.2 ml of cis-2,6-dimethylpiperidine and 68 ml of triethylamine were added, and the resulting mixture was stirred overnight. To the reaction solution, aqueous potassium carbonate solution was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/methanol = 20:1) to obtain 47.4 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethylpiperidyl)carbonylamino) propionate (yield: 46%).
LR-MS(m/z):523(M^+)
NMR(300MHz,$CDCl_3$, δ ppm): 1.19(6H,d,J=6.8),1.42-1.80(6H,m),3.80(3H,s),4.09-4.20(2H,m),4.36-4.46(2H,m), 4.70-4.77(1H,m),5.83-5.90(1H,m),7.37-7.50(4H,m),7.68-7.75(1H,m),8.30(1H,m)

Example 50

3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethylpiperidyl)carbonylamino)propanoic acid (50)

[0162]



(50)

[0163] In 1.0 ml of methanol, 38.3 mg of methyl 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethylpiperidyl)carbonylamino) propionate was dissolved, and 0.22 ml of 1N aqueous sodium hydroxide solution was added thereto, followed by stirring the resulting mixture overnight. To the reaction solution, 1N hydrochloric

acid was added and the resulting mixture was extracted with ethyl acetate. Organic phases were combined, washed with saturated saline, dried over anhydrous sodium sulfate and concentrated. The residue was reprecipitated from chloroform/ether to obtain 33.3 mg of 3-(4-((2,6-dichlorophenyl)carbonylamino)-2-oxohydropyrimidinyl)-2-((2,6-dimethylpiperidyl)carbonylamino)propanoic acid (yield: 89%).

LR-MS(m/z):508(M^+-H)

IR(KBr):3424,2942,1718,1658,1626,1563,1493,1432,1366,1305,1247,1192,790cm^{-1}

NMR(300MHz,CD_3OD,δppm):1.16(3H,d,J=6.8),1.20(3H,d,J=6.8),1.26-1.32(1H,m),1.40-1.53(1H,m),1.54-1.97(4H,m),4.08-4.20(3H,m),4.59-4.67(1H,m),4.70-4.76(1H,m),7.40-7.51(4H,m),7.98(1H,m)

Example 51

Inhibitory Effect by Compounds Against Binding between CS-1 Peptide and VLA-4-IgG Chimera Protein

[0164] In accordance with the teaching of a report (Humphrise,M.J. et al. J.Bio.Chem.,262,6886-6892(1987)), a conjugate between a peptide (Gys Leu His Gly Pro Glu Glu Ile Leu Asp Val Pro Ser Thr) containing CS-1 sequence and rabbit IgG (Sigma) was prepared. This was diluted with phosphate buffer (hereinafter referred to as "PBS(-)" for short), and the obtained solution was placed in the wells of a 96-well immunoplate (NUNC) in an amount of 100 μl/well, followed by leaving to stand the immunoplate at 4°C for 16 hours to immobilize the conjugate.

[0165] The wells were then washed twice with PBS(-), and 1% BSA solution in PBS, which BSA was heated at 80°C for 10 minutes, was placed in each well in an amount of 300 μl/well. The immunoplate was left to stand at 4°C for 3 hours, and then the solution in each well was removed by suction.

[0166] Each compound and VLA-4-IgG chimera protein (100 μl) were preliminarily reacted at room temperature for 20 minutes, and then the resulting mixture was allowed to react with the CS-1 peptide in each well at 30°C for 3 hours. Thereafter, non-bound VLA-4-IgG chimera protein was removed by suction, and each well was washed twice with 0.1% BSA-containing TBS buffer (150mM NaCl, 25mM Tris-HCl, 1 mM $MnCl_2$, PH7.4). To the bound VLA-4-IgG chimera protein, biotin-labelled anti-human IgG antibody (Vector) as a primary antibody was added, and then avidin-labelled horse radish peroxidase (Sigma) as a secondary antibody was added, thereby allowing the reactions. Then o-phenylenediamine as a substrate was added to color the reaction solution, and the absorbance at 490 nm was measured. From this absorbance, the binding inhibitory activity of each compound was determined. The inhibitory activities of the representative compounds are shown in Table 1.

Table 1

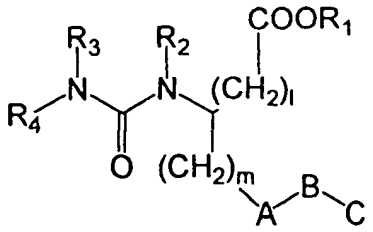
Compound No.	Inhibitory Activity (IC_{50}:nM)
28	3.8
32	0.97
35	2.4
37	3.5
50	4.5

Industrial Field

[0167] The novel urea derivatives according to the present invention have activities to inhibit cell adhesion via adhesion molecules, especially adhesion molecule VLA-4. Since the urea derivatives according to the present invention are excellent in the effect of inhibiting cell adhesion via adhesion molecules, they are useful as therapeutic drugs against various inflammatory diseases.

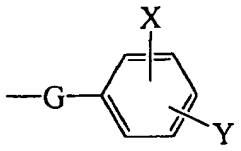
Claims

1. A urea acid derivative of the Formula I:



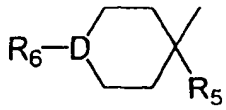
I

[wherein l represents an integer of 0 to 2; m represents an integer of 1 to 3; R_1 and R_2 independently represent hydrogen or C_1-C_6 linear alkyl; R_3 and R_4 independently represent hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole (excluding cases wherein C is represented by the Formula XIII:



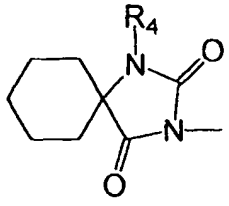
XIII

(wherein X and Y independently represent hydrogen, halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino or tetrazole; G may or may not exist, and when G exists, G is a nitrogen atom))
or represent Formula II:



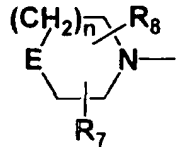
II

(wherein D represents a carbon atom or nitrogen atom; R_5 represents hydrogen, C_1-C_6 linear alkyl C_3-C_8 branched alkyl, C_1-C_6 linear N-alkylcarboxamide, C_3-C_8 branched N-alkylcarboxamide, or phenyl or N-phenylcarboxamide, this phenyl or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole (with the proviso that when C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), R_5 is C_1-C_6 linear N-alkylcarboxamide, C_3-C_8 branched N-alkylcarboxamide or N-phenylcarboxamide substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole); R_6 represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, or phenylsulfonyl, benzoyl or benzyl, this phenylsulfonyl, benzoyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole) (with the proviso that when C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), R_6 is phenylsulfonyl, benzoyl or benzyl, this phenylsulfonyl, benzoyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of methyl, cyano, nitro, amino and tetrazole);
R_2 and R_3 may cooperatively represent Formula III:



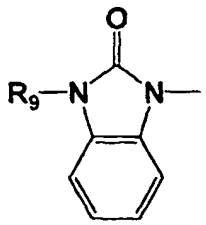
III

(wherein R_4 represents the same meanings as described above);
R_3 and R_4 may cooperatively represent (i) Formula IV:



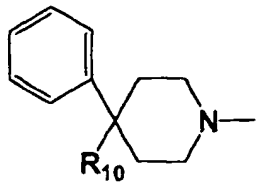
IV

(wherein n represents an integer of 0 to 4; E represents a carbon atom or nitrogen atom; R_7 and R_8 independently represent hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, pyrrolidine carbonyl, piperidine carbonyl, or phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide, this phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole (with the proviso that when C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), R_7 and R_8 independently represent pyrrolidine carbonyl, piperidine carbonyl, or phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide, this phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of methyl, cyano, nitro, amino and tetrazole)
or Formula V:



V

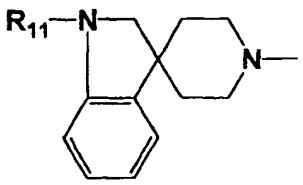
(wherein R_9 represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole),
(ii) Formula VI:



VI

(wherein R_{10} represents cyano, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylamide, C_3-C_8 branched alkylamide, C_5-C_7 cycloalkylamide, C_1-C_6 linear alkylsulfonylamine, C_3-C_8 branched alkylsulfonylamine, or benzamide, phenylsulfonylamine or benzylamino, this benzamide, phenylsulfonylamine or benzylamino being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole) (with the proviso that when C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), R_{10} is C_1-C_6 linear alkylsulfonylamine, C_3-C_8 branched alkylsulfonylamine, or phenylsulfonylamine substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole),

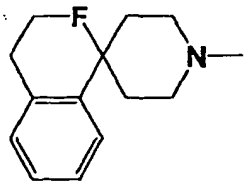
(iii) Formula VII:



VII

(wherein R_{11} represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, C_1-C_6 linear alkylsulfonyl, C_3-C_8 branched alkylsulfonyl, or phenylsulfonyl, benzyl or benzoyl, this phenylsulfonyl, benzyl or benzoyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazolc) (excluding cases where C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above),

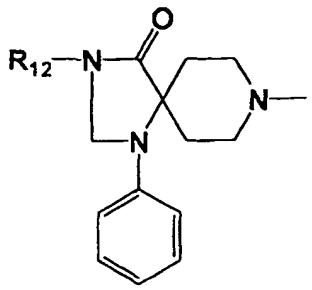
(iv) Formula VIII:



VIII

(wherein F represents a carbon atom, oxygen atom, sulfur atom or nitrogen atom; when F is a nitrogen atom, the substituent on said nitrogen atom is hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, C_1-C_6 linear alkylsulfonyl, C_3-C_8 branched alkylsulfonyl, or phenylsulfonyl, benzyl or benzoyl, this phenylsulfonyl, benzyl or benzoyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole) (excluding cases where C is represented by said Formula XIII (wherein symbols therein represent the same meanings as described above), or

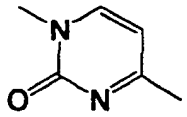
(v) Formula IX:



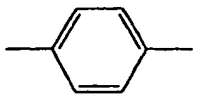
IX

(wherein R_{12} represents hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_6-C_{10} alkylcycloalkyl, or phenyl or benzyl, this phenyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole;

A is represented by Formula XI or XII:



XI



XII ;

B may or may not exist, when B exists, B represents amide or C_1-C_3 methylene chain;
C is represented by said Formula IV, VI, VII, VIII, IX or XIII (wherein symbols therein represent the same meanings as described above),
or a pharmaceutically acceptable salt thereof.

2. The urea derivative or a pharmaceutically acceptable salt thereof according to claim 1, wherein in Formula I, R_3 and R_4 independently represent said Formula II (excluding cases where R_3 and R_4 simultaneously represent said Formula II, and excluding cases where, when C is represented by said Formula XIII, R_5 is hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, or phenyl substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl, amino and tetrazole, and simultaneously R_6 is hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, or phenylsulfonyl, benzoyl or benzyl, this phenylsulfonyl, benzoyl or benzyl being substituted with 0 to 2 substituents selected from the group consisting of halogen, methoxy and hydroxyl); R_2 and R_3 cooperatively represent said Formula III; or R_3 and R_4 cooperatively represent (i) said Fromula IV (excluding cases where, when C is represented by said Formula XIII, R_7 and R_8 independently represent hydrogen, C_1-C_6 linear alkyl, C_3-C_8 branched alkyl, C_1-C_6 linear alkylacyl, C_3-C_8 branched alkylacyl, or phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide, this phenyl, phenylsulfonyl, benzoyl, benzyl, indole, benzamide or N-phenylcarboxamide being substituted with 0 to 2 substituents selected from the group consisting of halogen, methoxy and hydroxyl), (ii) said Formula VI (excluding cases where, when C is represented by said Formula XIII, R_{10} is cyano, C_1-C_6 linear alkyl, C_3-C_8 branched

alkyl, C_1-C_6 linear alkylamide, C_3-C_8 branched alkylamide, C_5-C_7 cycloalkylamide, or benzamide or benzylamide, this benzamide or benzylamide being substituted with 0 to 2 substituents selected from the group consisting of halogen, methyl, methoxy, cyano, nitro, hydroxyl and amino), (iii) said Formula VII (excluding cases where C is represented by said Formula XIII), or (iv) said Formula IX, the definitions of symbols other than stated above being the same as in claim 1.

3. A pharmaceutical comprising said urea derivative or a pharmaceutically acceptable salt thereof according to claim 1 or 2 as an effective ingredient.

4. An adhesion molecule inhibitor comprising said urea derivative or a pharmaceutically acceptable salt thereof according to claim 1 or 2 as an effective ingredient.

5. The adhesion molecule inhibitor according to claim 4, wherein said adhesion molecule belongs to integrin family.

6. The adhesion molecule inhibitor according to claim 5, wherein said integrin family is VLA-4.

7. The adhesion molecule inhibitor according to any one of claims 4 to 6, which is for against inflammatory disease.

8. The adhesion molecule inhibitor according to claim 7, wherein said inflammatory disease is an allergic disease.

9. A method for inhibiting an adhesion molecule, comprising administering an effective amount of said urea derivative or a pharmaceutically acceptable salt thereof according to claim 1 or 2.

10. The method according to claim 9, wherein said adhesion molecule belongs to integrin family.

11. The method according to claim 10, wherein said integrin family is VLA-4.

12. The method according to any one of claims 9 to 11, which is for against inflammatory disease.

13. The method according to claim 12, wherein said inflammatory disease is an allergic disease.

14. Use of said urea derivative or a pharmaceutically acceptable salt thereof according to claim 1 or 2 for the production of a pharmaceutical.

15. Use of said urea derivative or a pharmaceutically acceptable salt thereof according to claim 1 or 2 for the production of an adhesion molecule inhibitor.

16. The use according to claim 15, wherein said adhesion molecule belongs to integrin family.

17. The use according to claim 16, wherein said integrin family is VLA-4.

18. The use according to any one of claims 14 to 17, wherein said pharmaceutical or adhesion molecule inhibitor is for against inflammatory disease.

19. The adhesion molecule inhibitor according to claim 18, wherein said inflammatory disease is an allergic disease.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/07990

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[7] C07C275/26, C07D239/47, C07D401/12, C07D401/14, C07D403/12, C07D471/10, C07D491/107, C07D495/10, C07D233/54, A61K31/506, A61K31/175, A61K31/513, A61K31/55, A61P43/00, A61P29/00, A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[7] C07C275/26, C07D239/47, C07D401/12, C07D401/14, C07D403/12, C07D471/10, C07D491/107, C07D495/10, C07D233/54, A61K31/506, A61K31/175, A61K31/513, A61K31/55, A61P43/00, A61P29/00, A61P37/08

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAPLUS (STN), CAOLD (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PA	WO 01/32610 A1 (Kaken Pharmaceutical Co., Ltd.), 10 May, 2001 (10.05.01) (Family: none)	1-8,14-19
PA	WO 01/14328 A2 (Merck & Co., Inc.), 01 March, 2001 (01.03.01), & AU 2000-69093 A	1-8,14-19
PA	WO 01/21584 A1 (Genentech, Inc.), 29 March, 2001 (29.03.01) (Family: none)	1-8,14-19
A	WO 00/37429 A2 (Tanabe Seiyaku Co., Ltd.), 29 June, 2000 (29.06.00), & EP 1144365 A2	1-8,14-19
A	WO 99/20272 A1 (Merck & Co., Inc.), 29 April, 1999 (29.04.99), & US 6069163 A	1-8,14-19

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 December, 2001 (11.12.01)	25 December, 2001 (25.12.01)
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer
Facsimile No.	Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP01/07990

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 9~13
because they relate to subject matter not required to be searched by this Authority, namely:

Claims 9 to 13 pertain to a method for treatment of the human body by therapy and thus relate to a subject matter which this International Searching Authority is not required, under the provisions of Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest
☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)